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Use of non-invasive intracranial pressure pulse waveform to monitor patients with End-Stage Renal Disease (ESRD)

Short title: Intracranial pressure in patients with ESRD

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Abstract

End-stage renal disease (ESRD) is treated mainly by hemodialysis, however, hemodialysis is associated with frequent complications, some of them involve the increased intracranial pressure. In this context, monitoring the intracranial pressure of these patients may lead to a better understanding of how intracranial pressure morphology varies with hemodialysis. This study aimed to follow-up patients with ESRD by monitoring intracranial pressure before and after hemodialysis sessions using a noninvasive method. We followed-up 42 patients with ESRD in hemodialysis, for six months. Noninvasive intracranial pressure monitoring data were obtained through analysis of intracranial pressure waveform morphology, this information was uploaded to Brain4care® cloud algorithm for analysis. The cloud automatically sends a report containing intracranial pressure parameters. In total, 4881 data points were collected during the six months of follow-up. The intracranial pressure parameters (time to peak and P2/P1 ratio) were significantly higher in predialysis when compared to postdialysis for the three weekly sessions and throughout the follow-up period (p<0.01) data showed general improvement in brain compliance after the hemodialysis session. Furthermore, intracranial pressure parameters were significantly higher in the first weekly hemodialysis session (p<0.05). In conclusion, there were significant differences between pre and postdialysis intracranial pressure in patients with ESRD on hemodialysis. Additionally, the pattern of the intracranial pressure alterations was consistent over time suggesting that hemodialysis can improve time to peak and P2/P1 ratio which may reflect in brain compliance.

Keywords: Chronic kidney disease, brain compliance, intracranial pressure, hemodialysis, dialysis disequilibrium syndrome

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1. Introduction

Chronic kidney disease (CKD), a leading cause of mortality and morbidity and a growing public health problem worldwide [1], is a complex disease that requires multiple treatment approaches [2].

Hemodialysis (HD) has become the predominant renal replacement therapy (RRT) in the world [3]. However, HD is associated with frequent complications, including hypotension and muscle cramps, in addition to postdialysis complaints of headache, fatigue, and inability to concentrate, which may significantly affect patients' quality of life [4]. Mild signs and symptoms like headache, nausea, and muscle cramps are often attributed to volume depletion due to excessive ultrafiltration, but may represent a milder but not diagnosed form of dialysis disequilibrium syndrome (DDS) [5].

Even though maintenance HD has been a routine procedure for over 50 years, the exact mechanism of DDS remains poorly understood [6] and the syndrome manifests as neurologic symptoms and signs related to osmotic fluid shifts [5]. Cerebral edema and increased intracranial pressure (ICP) are the primary contributing factors to this syndrome and are the targets of therapy [6]. Neurologic manifestations progress sequentially as cerebral edema worsens and ICP rises and, if not promptly recognized and managed, can lead to coma and even death [7].

ICP monitoring could assist in the early diagnosis of DDS, but the methods in use are highly invasive, costly, and carry complication risks. However, a noninvasive method based on volumetric skull changes detected by a sensor has been developed [8]. This method allows for quick and safe access to ICP pulse waveform morphology, which is correlated with brain compliance [9].

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This study aimed to follow-up patients with end-stage renal disease (ESRD) by monitoring ICP before and after HD sessions using a noninvasive method to assess ICP variations during HD treatment.

2. Materials and Methods

2.1 Participants

This is a prospective longitudinal study of 42 patients aged ≥ 18 years with end-stage renal disease (ESRD) from a single RRT center who received HD periodically, three times per week with two one-day intervals and one two-day interval between sessions, for six months. HD session length ranged from three to four hours depending on the patient and his/her condition. The authors declare that they adhered to the Declaration of Helsinki. All participants received information about the study and provided written informed consent. The study was approved by the local Research Ethics Committee (process number: 1.834.627).

The clinical characteristics of participants including age, gender, underlying disease, start of treatment, and comorbidities were retrieved from the electronic medical records of the RRT center.

2.2 Intracranial pressure (ICP) and brain compliance monitoring

In total, 4881 data points were collected during the six months of follow-up. The noninvasive ICP monitoring equipment was provided by Brain4care® (São Paulo, SP, Brazil). This noninvasive method was validated by comparison with the invasive ICP monitoring method [8,10].

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Predialysis monitoring sessions were done before the HD session in a private room with the patient seated in a chair similar to the one used in the HD session while ICP was monitored for 1 to 3 min. The patient should remain still during signal acquisition and the same procedure was performed after the HD session. Figure 1 shows a flowchart of how this search was conducted.

Figure 1. Flowchart of this research.

Figure 1. CKD: chronic kidney disease; ESRD: end-stage renal disease; HD: hemodialysis; ICP: intracranial pressure.

Monro-Kellie doctrine states that the skull does not expand after the fontanels are closed. However, for the development of the ICP monitor, it was proven that the skulls, even those of adults, have volumetric changes, as a result of pressure variations and the noninvasive monitoring of ICP is based on the assessment of these changes in bone structure [11].

To perform the monitoring, a sensor that detects the micrometric deformations of the skull bones is attached to a plastic headband strapped around the patient's head. The device filters, amplifies and digitizes the signal from the sensor before sending it to a computer [8].

Noninvasive ICP monitoring data were obtained through analysis of ICP waveform morphology. The ICP waveform is a modified blood pressure wave with three distinct peaks. The first peak (P1, or 'percussive wave') is the result of arterial pressure transmitted from the choroid plexus. The second peak (P2) signifies brain compliance and the last peak (P3) is the result of the aortic valve closure. Thus, under normal ICP conditions, the amplitude of the peaks is such that P1>P2>P3 [12,13]. However as brain compliance

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decreases and the ICP increases, the amplitude of the wave also increases and the P2 component of the wave exceeds P1 and P3 [14].

Following the ICP monitoring, the software saved the data to files that were later uploaded to Brain4care® for analysis. The result is a report containing the time to peak (TTP) and P2/P1 ratio. TTP was defined as the time at which the ICP curve reaches its tallest peak, either P1 or P2, starting from the start of the curve. The P2/P1 ratio assesses brain compliance and was defined as the ratio between the amplitudes of peaks P2 and P1 (R=AmpP2/AmpP1). Brain compliance is normal when R < 1.0 (P2<P1) and abnormal when R > 1.0 (P2>P1).

2.3 Statistical analysis

Clinical characteristics are expressed as mean ± standard deviation (SD) for continuous variables and relative frequency (%) for categorical variables. First, the mean ± SD of noninvasive ICP parameters (TTP and P2/P1 ratio) were calculated separately for the three weekly HD sessions (1st, 2nd, and 3rd) for each month of follow-up. Next, the normality of data distribution was assessed by examining the skewness and kurtosis. All coefficients were between −2 and +2 and the data were thus normally distributed.

Predialysis and postdialysis noninvasive ICP parameters were compared using the Student's t-test for paired samples. Besides, TTP and P2/P1 ratio were also compared between the three weekly HD sessions using repeated measures analysis of variance (ANOVA) and Tukey multiple comparison tests. A *p*-value of <0.05 was considered statistically significant. All analyses were performed using SPSS version 17.0® for Windows (SPSS Inc., Chicago, IL, USA).

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3. Results

Table 1 shows the baseline characteristics of the study participants.

Table 1. Clinical characteristics of the study patients*.

Clinical parameter	**Value**
Age (years)	55.8 ± 16.5
Age ≥ 60 years (%)	50.0
Female gender (%)	45.2
CKD cause (%)	
undetermined	23.8
multifactorial	11.9
diabetic nephropathy	11.9
chronic glomerulonephritis	11.9
polycystic kidney disease	9.5
hypertensive nephrosclerosis	4.8
other	26.2
Comorbidities (%)	
systemic arterial hypertension	64.3
diabetes mellitus	21.4
Mean HD session length (min)	220.0 ± 23.9
HD session length ≥ 240 min (%)	52.4
Mean HD time (years)	4.8 ± 4.8

*Sample size: 42 patients with CKD on regular hemodialysis.
CKD, chronic kidney disease; HD, hemodialysis.
Values are mean ± standard deviation or relative frequency (%).

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The results of the intracranial pressure (ICP) pulse waveform monitorings are shown in Figure 2. The parameters TTP and P2/P1 ratio were generally higher in the predialysis moment compared to the postdialysis moment. This change was repeated over time and a statistically significant difference was demonstrated in all evaluated sessions and months ($p<0.01$, paired Student's t-test).

Still, in Figure 2, a second analysis comparing ICP parameters between the three weekly hemodialysis sessions over the six months of follow-up showed no significant differences in predialysis and postdialysis measurements. However, when all monitorings from each HD session (1st, 2nd, and 3rd weekly session) were pooled, there were significant differences in predialysis TTP and P2/P1 ratio with higher non-invasive ICP parameter values in the first session of the week (Figure 3) ($p<0.05$, repeated-measures ANOVA followed by the Tukey's post-hoc test).

Figure 2. Predialysis and postdialysis noninvasive intracranial pressure (ICP) parameters at the three weekly hemodialysis sessions over the six months of follow-up.

Figure 2. A) Time to peak (TTP). B) P2/P1 ratio. Differences between predialysis and postdialysis intracranial pressure parameters were analyzed by paired Student's t-test (*$p<0.01$). Differences in TTP and P2/P1 ratio between the three weekly hemodialysis sessions were analyzed by repeated-measures ANOVA but were not significant ($p>0.05$). Data are presented as Mean ± SD.

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Figure 3. Comparison of predialysis and postdialysis noninvasive intracranial pressure (ICP) parameters according to the hemodialysis sessions over the six months of follow-up.

Figure 3. (A) Time to peak (TTP). (B) P2/P1 ratio. Box-plots illustrate the median and interquartile range of the noninvasive intracranial pressure parameters at the three weekly hemodialysis sessions (1st, 2nd, and 3rd) over the six months of follow-up (*p<0.05, repeated-measures ANOVA followed by the Tukey's post-hoc test).

4. Discussion

The main finding of this study was the significant difference detected between predialysis and postdialysis noninvasive ICP parameters (TTP and P2/P1 ratio) over the six months of follow-up (Figure 2). These parameters obtained through analysis of ICP waveform morphology. According to Nucci et al. (2016), changes in ICP waveform morphology can reflect changes in ICP whereas ICP wave morphological analysis can in turn predict the ICP measurements of invasive methods [15].

Considering that in general the parameters of non-invasive ICP were higher in the predialysis moment, it is suggested that the removal of fluids promoted by HD may be beneficial in improving cerebral compliance of patients with ESRD. Nevertheless, HD is associated with frequent complications, some of them involve the increased intracranial pressure, such as DDS [6].

Intradialytic hypotension is the commonest complication among HD patients [16–20] and may precede DDS. The symptoms like headache, nausea, and muscle cramps experienced by some patients of the current study during follow-up may represent a milder

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but not diagnosed spectrum of DDS [5]. Our understanding of the pathophysiology of DDS has improved since its initial description and it is now evident from animal and human studies that DDS is associated with the development of cerebral edema and increased ICP [21,22].

At first DDS was believed to occur only in patients with acute kidney injury when hemodialysis was first initiated, but it has also been reported in patients with CKD [7,23].

According to Castro (2001), DDS can be prevented in patients with very high plasma urea levels by performing low-efficiency dialysis sessions of brief duration, reducing the interdialytic interval, and adding hypertonic solutions such as mannitol in the dialysate, which contribute to reduce cerebral edema [24].

In the current study, we showed that noninvasive ICP parameters (TTP and P2/P1 ratio) were higher in the first HD session of the week (Figure 3). Foley et al. (2011) found that in patients receiving maintenance HD, adverse events including all-cause mortality, myocardial infarction, and hospital admissions occurred more frequently on the day after the long interdialytic interval (1st weekly session) than on other days. We believe that this long (two-day) interdialytic interval contributes to higher interdialytic weight gain (IDWG) and changes in ICP [25].

IDWG is the result of salt and water intake between two HD sessions and is influenced by several factors. It is recommended that IDWG does not exceed 4.5% of 'dry body weight' [26]. Recently, it has been reported that patients with IDWG ≥ 5.7% and 4%, respectively, are at an elevated risk for mortality and increased risk for fluid-overload hospitalization [27].

We hypothesize that patients with an IDWG ≥ 4% have worse brain compliance and greater chances of complications, because ICP is derived from cerebral blood and

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parenchyma and cerebrospinal fluid (CSF) circulatory dynamics, an increase in any of these components (blood, CSF, or parenchyma) may increase ICP [28,29].

A higher IDWG is associated with complications including higher predialysis blood pressure[30,31] , intradialytic hypotension as a result of rapid fluid removal during the HD session [32] , and increased mortality [33,34] , and it may also be related to changes in ICP. Ipema et al. (2016) highlighted the importance of personalized advice on fluid and sodium restriction in HD patients [35].

This work was able to demonstrate through a non-invasive method that changes in the ICP of patients undergoing hemodialysis occur, and that these changes are repeated over the months. It is suggested that hemodialysis can improve the parameters of ICP that reflect brain compliance, however, future studies are warranted that examine the causes of ICP alterations, especially considering that prolonged ICP elevation is associated with poor neurocognitive outcomes [36]. Besides that, we show that the noninvasive ICP parameters TTP and P2/P1 ratio were higher in the first weekly HD session than in the second and third sessions, which may happen as a function of the time gap between the last and the first session of the week.

As previously exposed, the noninvasive method used in this study was validated by comparison with the invasive ICP monitoring method [8,10] and has been used in the study of several situations, physiological and pathological, involving the central nervous system [37–41]. Based on this context, the routine uses of non-invasive ICP monitoring in RRT centers could contribute to the clinical evaluation of patients with ESRD.

Through this unprecedented study, using a non-invasive method, it was possible to understand how the ICP of patients with ESRD behaves. Results of ICP wave morphology analysis of patients with ESRD followed-up for six months by noninvasive ICP monitoring

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revealed significant differences between predialysis and postdialysis ICP parameters. Also, the pattern of ICP alterations was consistent throughout the study.

4.1 Limitations of the study

Due to the dynamics used to carry out this study, it was not possible to detect complications and correlate them to the ICP. New studies that evaluate patients individually and for a longer time in each dialysis session could explain this issue.

5. Acknowledgment

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001.

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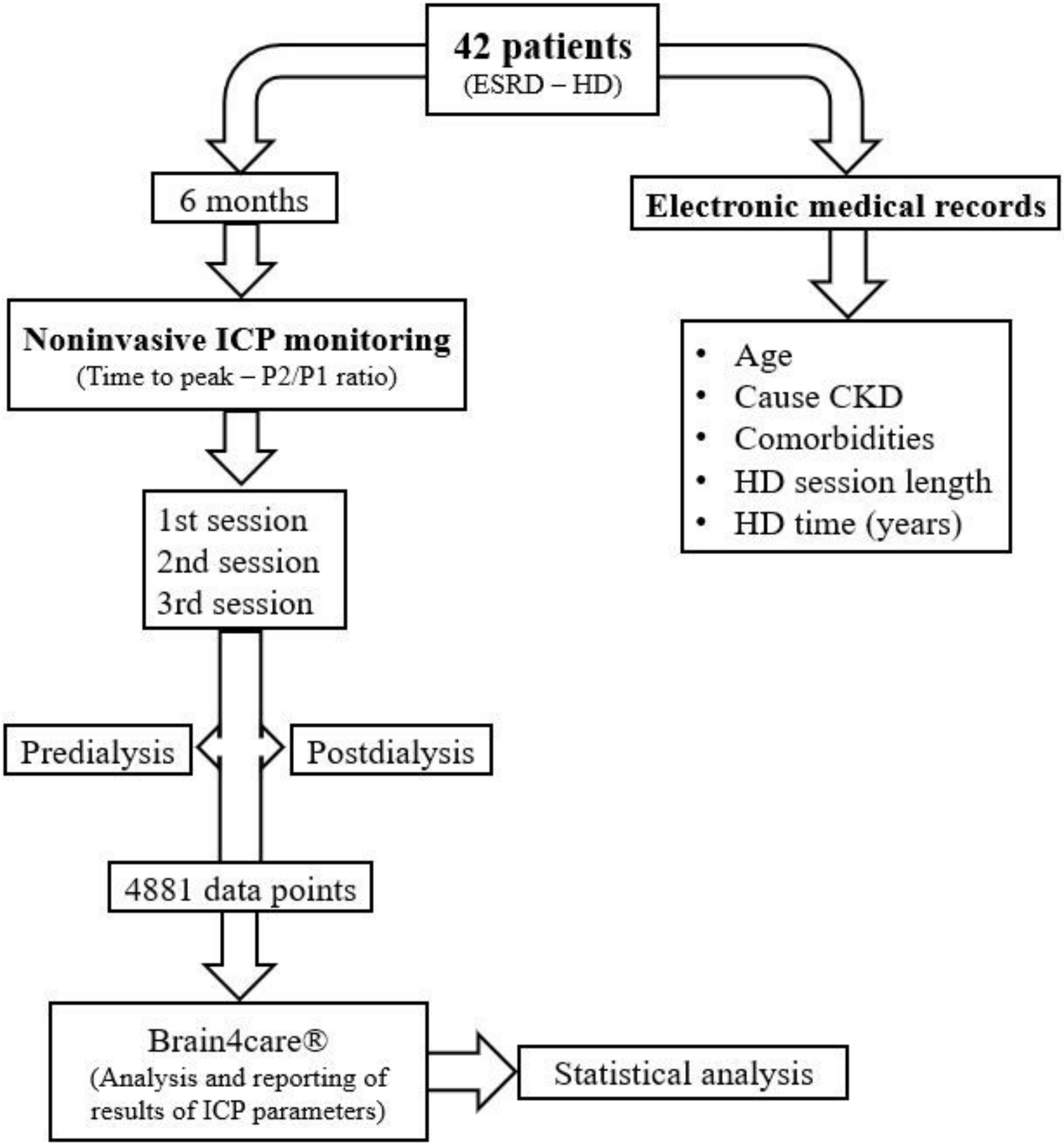
42 patients
(ESRD – HD)
6 months
Electronic medical records
Noninvasive ICP monitoring
(Time to peak – P2/P1 ratio)
• Age
• Cause CKD
• Comorbidities
• HD session length
• HD time (years)
1st session
2nd session
3rd session
Predialysis
Postdialysis
4881 data points
Brain4care®
(Analysis and reporting of results of ICP parameters)
Statistical analysis

Figure 1

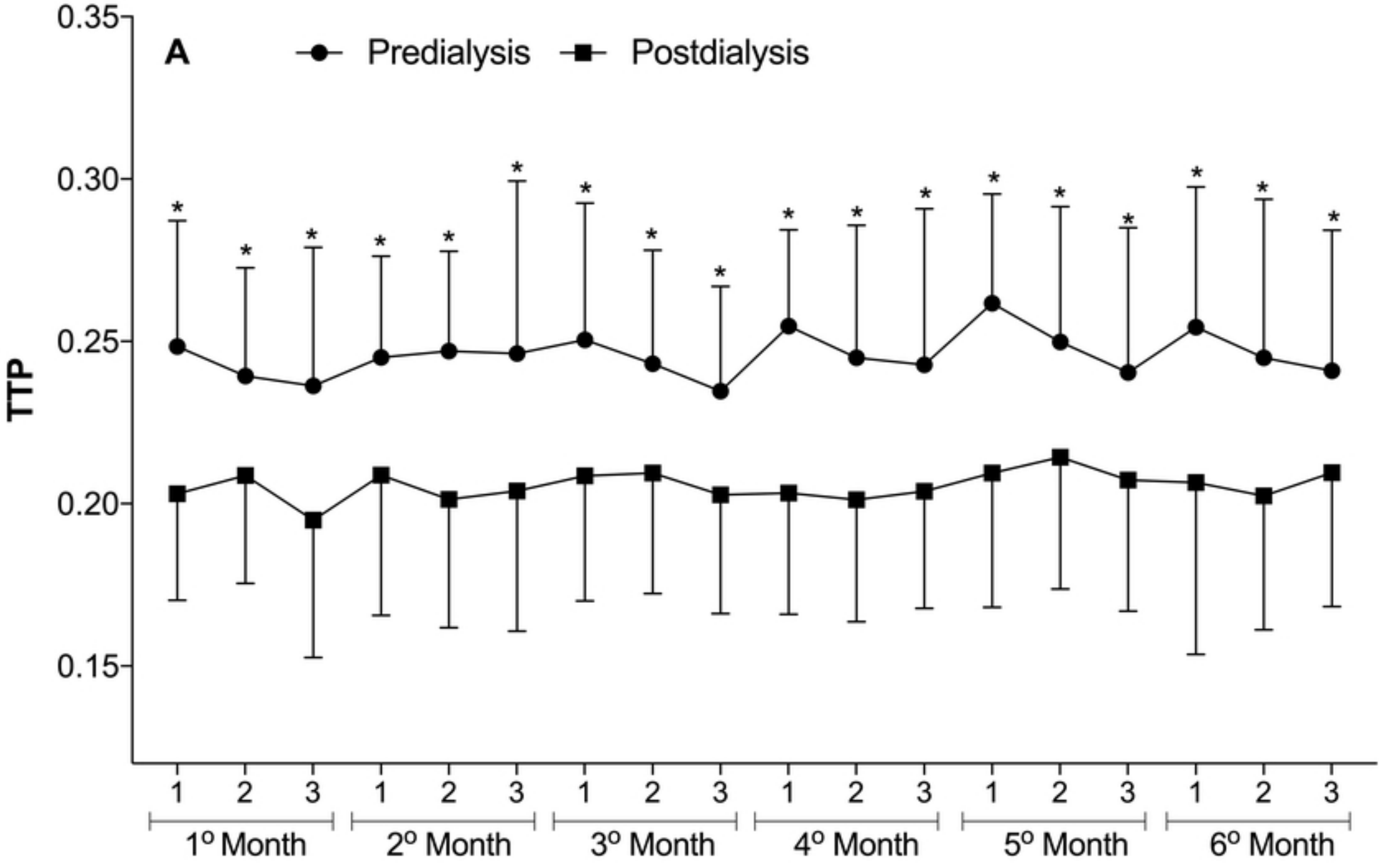
A
Predialysis
Postdialysis
TTP
0.35
0.30
0.25
0.20
0.15
1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3
1º Month
2º Month
3º Month
4º Month
5º Month
6º Month

Figure 2A

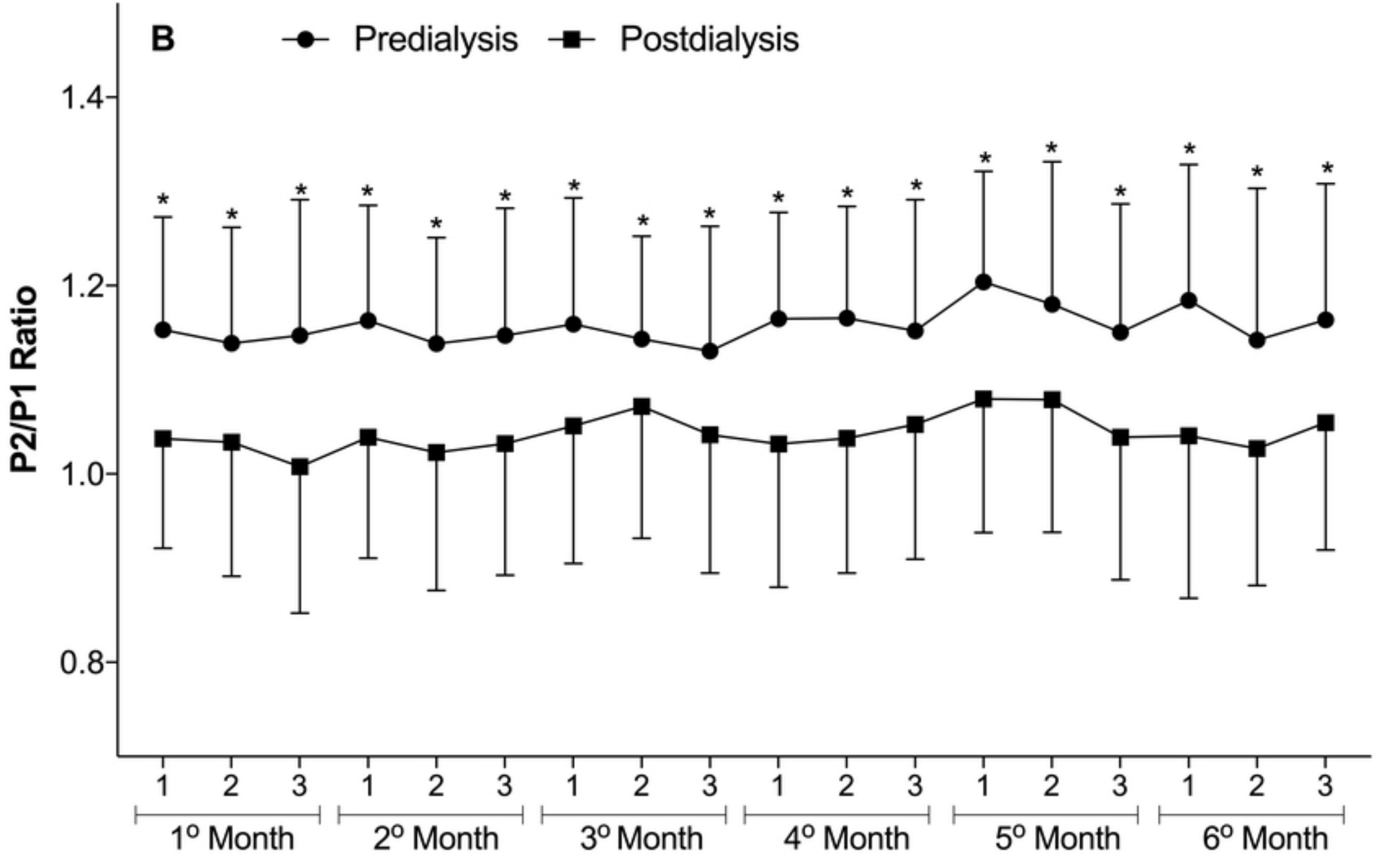
B
Predialysis
Postdialysis
P2/P1 Ratio
1.4
1.2
1.0
0.8
1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3
1º Month
2º Month
3º Month
4º Month
5º Month
6º Month

Figure 2B

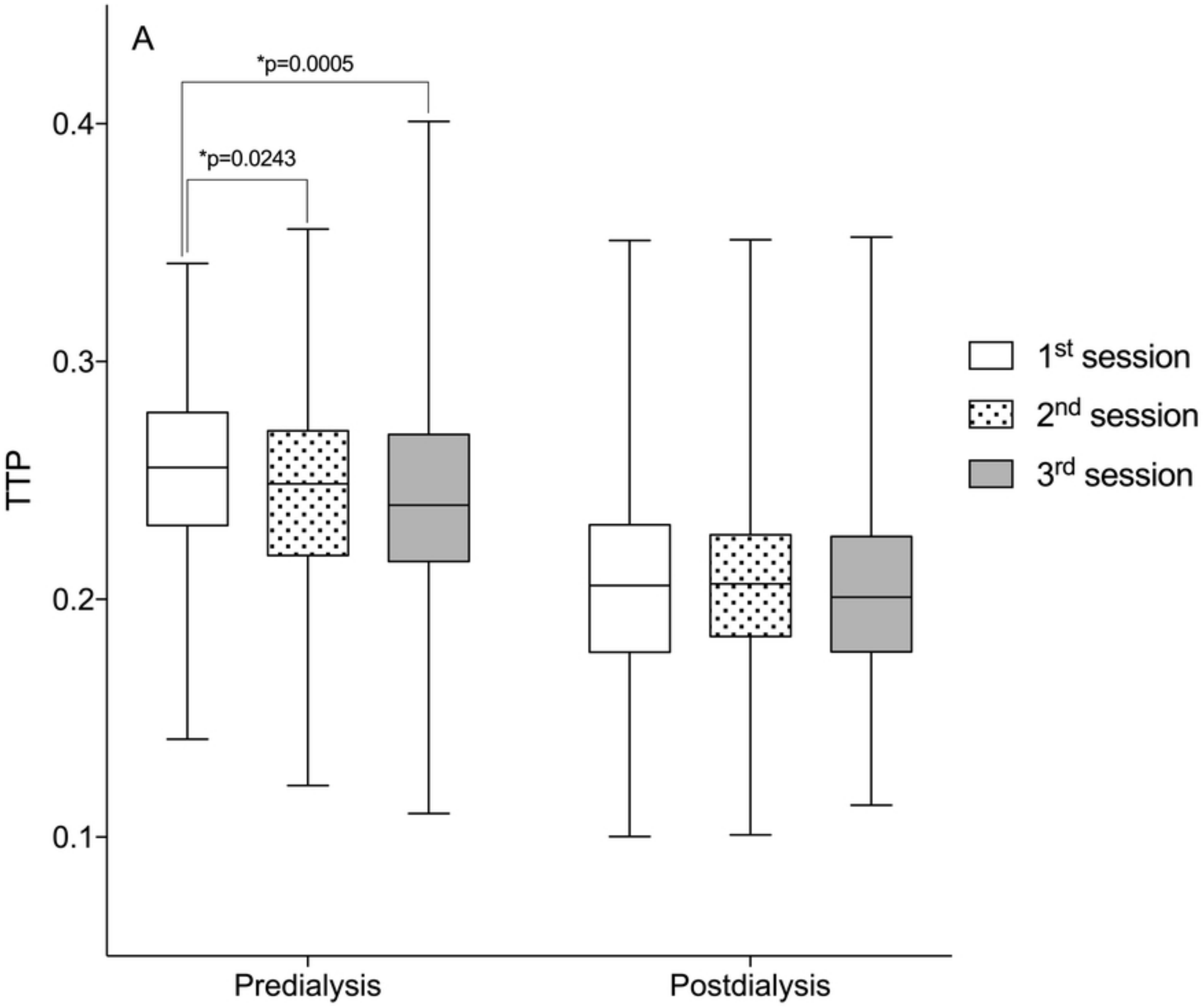
A
*p=0.0005
*p=0.0243
0.4
0.3
0.2
0.1
TTP
1st session
2nd session
3rd session
Predialysis
Postdialysis

Figure 3A

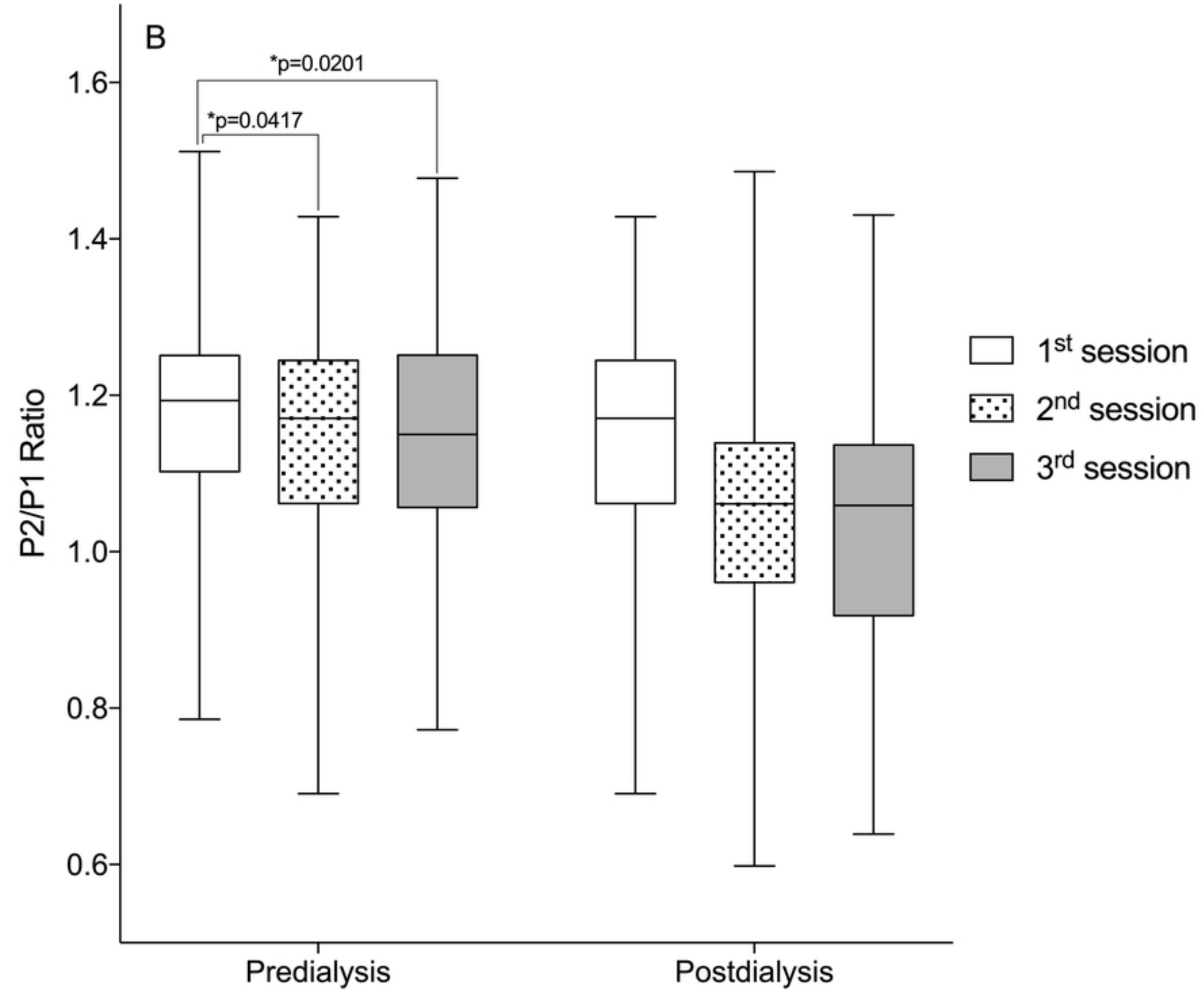
B
*p=0.0201
*p=0.0417
P2/P1 Ratio
1.6
1.4
1.2
1.0
0.8
0.6
1st session
2nd session
3rd session
Predialysis
Postdialysis

Figure 3B