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Value Of Lung Ultrasound And Serum Level Of Brain Natriuretic Peptide In Diagnosis Of Asymptomatic Pulmonary Congestion Among Saudi Pediatric Hemodialysis Patients

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ABSTRACT

***Background**: Depending on clinical assessment, determining the ideal dry weight (DW) to minimize volume overflow in hemodialysis (HD) patients is imprecise since hypervolemia symptoms appear only when severe dehydration occurs. **Objective**: To evaluate the diagnostic accuracy of serum level of brain natriuretic peptide (BNP) and its correlation with lung ultrasound (LUS) in detecting the presence of asymptomatic pulmonary congestion as a sign of residual v[1]olume overload in HD patient. **Patients and Methods:** A prospective observational study was conducted on 20 HD pediatric patients withasymptomatic pulmonary manifestation who underwent LUS and BNP leveling before and after HD session, LUS was considered positive when B-line score (BLS) >10. Volume load parameters were also evaluated before and after HD. **Results:** the reduction in mean BNP after HD session was significant as BNP levels reduced from (219.5±67.802) pg/ml to (116.75±50.772) pg/ml, with significant positive correlation between post-dialysis BNP and BLS ($p< 0.001$, r 0.914).**Conclusion**: LUS lung congestion was present in a large number of patients who were clinically euvolemic, without clinical signs of overhydration, and who were deemed to be at goal DW at the end of the HD session. This implies that a patient can continue to experience residual volume overload even after reaching their purported goal DW. In the event that LUS is not an option, BNP leveling might be useful.*

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INTRODUCTION

In the absence of hypo- or hypervolemia, DW is a volumetric illness. An precise extravascular lung water calculation is essential to avoiding these effects since faulty DW estimation can lead to chronic hypovolemia and hypervolemia, which can cause long-term cardiovascular problems or chronic dehydration [(1)].

Several clinically euvolemic patients who were believed to be at goal DW displayed lung congestion at LUS, as demonstrated by bioimpedance analysis (BIA), without any signs of oedema, dyspnea, or overhydration [(2)].

Pulmonary microcirculation congestion, common in HD patients but often asymptomatic and challenging to diagnose, can be evaluated by LUS (3). A BLS, which is used to quantify pulmonary congestion, can be calculated by identifying the echo detectable artifact known as the B line, which is caused by the air-water interface generated by the increased pulmonary extravascular volume [(4)].

Furthermore, BNP serum levels could be useful as a sensor for overhydration; despite being subject to a number of factors, they could be seen as an indicator of myocardial cell distension in response to circulating volume overload [(5)].

The study aimed to evaluate the diagnostic accuracy ofserum level of BNP and its correlation with LUS in detecting the presence of asymptomatic pulmonary congestion as a sign of residual volume overload in HDpatient.

SUBJECTS AND METHODS

This prospective observational study was carried out from July 2022 to December 2022, in the Pediatric Nephrology Unit of the Makkah Hospital, Saudi Arabia.
20 chronic hemodialysis children 3-18 years of both sexes on thrice weekly schedule on HD Unit for at least 6 months with clinical stability for at least 3 months with asymptomatic pulmonary manifestation wereincluded.

Exclusion criteria:

- Patients with unstable clinical conditions.
- Patients with current infections.
- Patients with volume or pressure overload due to other causes than fluid overload as left ventricular dysfunction with EF< 50%, cardiac anomalies, pulmonary hypertension, clinical evident heart failure.
- In line with previous study [(6)], patients with diseasessuch as co-existing lung fibrosis, atelectasis, lymphangitis, interstitial lung disease, heart failure, and acute respiratory distress syndrome may have B lines that signify underlying pathology and cloud the evaluation of fluid overload.

Patients were dialyzed using polysulfone hollow fibre dialyzers appropriate for their surface area (Fresenius F3 = 0.4 m^2, F4 = 0.7 m^2, F5 = 1.0 m^2, and F6 = 1.2 m^2) on Fresenius 4008B and 5008s dialysis machines (Bad Homburg, Germany) at blood flow rate = 2.5 weight (kg) + 100 ml/min. The dialysis solutions contained bicarbonate.

The following procedures were applied to allpatients:

Complete history taking: including age, sex, residence, causes of CKD, duration of dialysis, and useof antihypertensive drug.

Clinical examination: including vital signs, anthropometric measurements and urine output.

Systemic examination, which includedneurological, gastrointestinal, and chest checks.

Pre- and post-dialysis measurements were taken to determine the patients' level of hydration. These measurements included clinical parameters of fluid overload (dyspnea at rest, orbital edema, weight gain, hypertension, and chest crepitation), interdialytic weight gain (IDWG), post-dialysis weight, dry weight, and both SBP and DBP. Hypertension was defined as blood.

Regular laboratory tests such as complete blood count, blood urea, serum creatinine, Na, K, Ca, Ph, andPTH.

Specific investigations: serum BNP levels with enzyme-linked immunosorbent assay (ELISA) were assessed 15 minutes before and 15 minutes after HD session.
ECHO for exclusion criteria.

LUS: LUS measurements were performed 15 minutes before and after the HD session with the available sonography equipment (GE LOGIQ V5 pro series ultrasound machine with linear probe 3-5 HZ). Patients had the examination while lying flat. In the midaxillary, anterior axillary, midclavicular, and parasternal spaces of the right and left hemithoraces, from the second to the fourth (on the left) and to the fifth(on the right) intercostal spaces, twenty-eight distinct lung windows were scanned [7]. The B-line sign was described as an echogenic artefact with a small beginning on the pleural line, deepening to the inferior border of the screen, and consistent with respiratory movements with **Yontem et al.** [8].

The aggregate of the artefacts found in the 28 examined sectors yielded the total number of B-lines (BLS). LUS exams were regarded as negative for pulmonary congestion when BLS was ≤10 (LUS-) and positive for pulmonary congestion when BLS was > 10(LUS+), assuming a BLS cut-off value of 10 for the test
(6).

Ethical approval:

Medical Ethics Committee approved this study. Following receipt of all information, all the caregivers of the participants provided written consent. Throughout the study, the Helsinki Declaration was observed.

Statistical Analysis

Using the SPSS V.28 programme, data were analysed using the proper 2-sided tests with a significance level of 0.05. Quantitative data were displayed as mean±standard deviation, whilst categorical data were shown as numbers and percentages. ROC curve was used to the test significance of the diagnostic accuracy of BNP.

RESULTS

Patient’s data:

20 patients were enrolled, 12 patients were males,median age was 14.6 years, all received maintenance 3 HD sessions weekly for 3-4 hours with the main duration of HD 33±43.7 months, all growth parameterswere decreased according to age and sex.
The most frequent source of ESRD among studied patients was obstructive uropathy (8) followed by unknown etiology (5).

13 patients were normotensive and reached dry weight,14 patients had normal Echo finding, the others (6) patients had left ventricular hypertrophy (LVH). The difference between patients with normal Echo finding and those with LVH in SPB, DPB, BLS and serum BNPwere not significant.

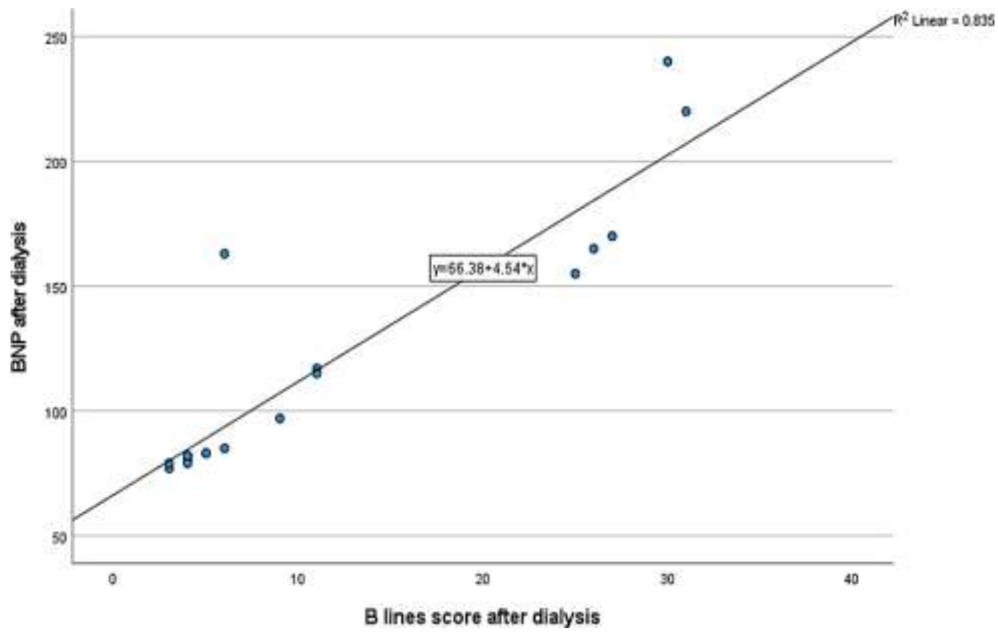
Volume load parameters measured before and afterdialysis:
The measurements before dialysis indicated increase in volume overload, while the disparities between pre- and post-dialysis values showed that hemodialysis decreased volume overload status and all of the tested variables had significant values as the meandecrease in weight, SBP and DBP were significant(Table 1).

Before – after dialysis	Mean	SD	Diff.	Corr. (r)	p-valueǂ	t-test	p-value¥
weight before (kg) Weight after (kg)	34.495 32.89	9.428 9.097	1.6	0.997	<0.001	9.34	<0.001
Systolic pressure before (mmHg) Systolic pressure after (mmHg)	110.75 96	21.106 18.61	14.8	0.966	<0.001	11.51	<0.001
Diastolic pressure before (mmHg) Diastolic pressureafter (mmHg)	70.75 57.5	14.714 15.347	13.3	0.935	<0.001	10.87	<0.001

Change in both BLS and BNP with dialysis:
The reduction in both mean B-line score and mean BNP after dialysis session was significant among DW patientsand among non-DW patients. Moreover, the difference between the two groups in the reduction of B-line score was significant, but in the reduction of BNP was not significant (Table 2).

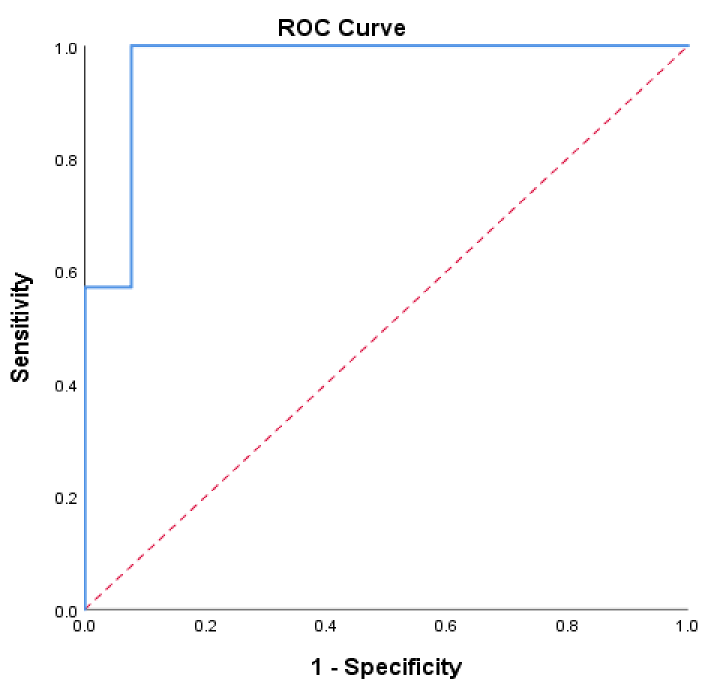
Indicator		Dry weight (n=15)		p-value¥	Non-dry weight (n=5)		p-value	Overall p-valueǂ
		Mean	SD		Mean	SD		
B line score	Before	12.7	3.8	<0.001*	39.3	10.4	0.002*	<0.001*
	After	4.9	2.1		22.7	8.96		
BNP (pg/ml)	Before	184.6	51.7	<0.001*	284.3	40.9	0.008*	0.478
	After	90.1	23.9		166.3	51.14		

Correlation between both BLS and BNP with each other and with other indices
Correlation of both predialytic BNP and BLS with other indices as IDWG, SPB and DBP were significantly positive,also correlation between both post-dialysis BNP and BLS with difference between post dialysis weight and DW, SBP and DBP were significantly positive. As regard correlation between BNP and BLS, there was no significant correlationin pre-dialysis setting (r 0.276, p 0.064), however the correlation in post-dialysis setting was significantly positive (r 0.914, p< 0.001) (Figure 1).



Cut-off value of BNP for prediction of pulmonary congestion

The area under the curve was significantly higher than the area of the chance (0.967 vs. 0.5, $p<0.001$). The best BNP cut-off value for predicting pulmonary congestion was shown to be 100 pg/ml (sensitivity 100, specificity 92.3, positive predictive value 87.5, negative predictive value 100 and accuracy 95) (Figure 2).



All patients were subdivided into DW and non DW groups according to clinical parameters of volume overload, blood pressure and documented DW, also into pulmonary congestion (LUS+)

and no pulmonary congestion accordingto BLS as BLS> 10 indicate pulmonary congestion.

Table 3 shows that 3 patients who reached target dry weight post-dialysis had residual pulmonary congestion.

BNP (pg/ml)		**No pulmonary congestion(LUS-) (n = 13)**		**nonary congestion(LUS+) (n =7)**		**p-value**
BNP before, mean ± SD		201.15	68.073	253.57	56.621	0.1
BNP After, mean ± SD		88.69	22.845	168.86	47.39	0.003*
ght, number(%)	Dry	12	92.3	3	42.9	0.031*
	Non	1	7.7	4	57.1	

DISCUSSION

A clinical examination at the patient's bedside has traditionally been used to determine their level of hydration. It may, however, be criticized in greater depth. There is currently no gold standard for determining the DW or a validated clinical score to assess hydration status in HD patients [(9)].

This study demonstrates that even in HD patients who do not exhibit any overhydration-related clinical symptoms, the presence of pulmonary congestion as determined by lung ultrasonography is fairly common. In fact, 7 out of 20 patients, or 35%, showed up with BLS > 10 and BNP levels > 100 pg/mlat the end of the HD session, without any signs of edema, dyspnea, or high blood pressure. Three patientsalso attained their reported dry weight. This finding is consistent with information from other studies, such as that of Giannese et al. (2), which showed that some patients who were clinically euvolemic and thought to be at target dry weight showed lung congestion at LUS in the absence of edema, dyspnea, and over-hydration as determined by BIA or impaired left ventricular function.

This implies that even after a patient reaches their alleged target weight, they may still be experiencing a residual volume overload that may be detected by LUS evaluation. If LUS is not an option, BNP levelling may be able to provide some assistance.Therefore, it would be crucial for LUS to play a significant part in clinical practise and integrate into the nephrologist's understanding.

Echo was done for each patient by an expertpediatric cardiologist, 14 patients had normal Echo findings and 6 patients revealed LVH.

Our findings demonstrated no difference in BLS or BNP levels between the LVH and non-LVH groups. Similarly, Mouche et al. (10) found no significant differences between patients with or without LVH and pre-HD BNP levels. Furthermore, Giannese et al. (2) found no difference between LUS+ and LUS- persons when cardiac disease, such as LVH, is taken into account. In contrast, Vaičiūnienė et al. (11) discovered that LVH patients were dehydrated based on BIA tests. Patients with LVH exhibited significantly more B lines on lung US before and after HD, and their BNP levels were more than three times higher. Both before and after HD, LVH patients had higher SBP.

In terms of mean B-line scores, there was ahighly significant drop in the overall number of B-lines following the HD sessions. Before dialysis, the mean total number of B-lines was (22±14.59); after dialysis, it was (11.1±10.22). Both the dry weight group (p< 0.001) and the non-dry weight group (p< 0.001) saw substantial decreases in B-line scores following dialysis. The mean B-line scores of the dry-weightgroup were lower before dialysis (12.7± 3.8) than thoseof the non-dry-weight group (39.3±10.4). The mean B-line scores of the dry-weight group (4.9 ± 2.1) were lower than those of the non-dry-weight group afterdialysis (22.7 ± 8.96), and

this difference was statistically significant (p< 0.001).
These findings supported those of Fu et al. (6), who discovered that in the dry weight group, mean B-line scores reduced from 23.5 before hemodialysis to 8.5 afterward. The mean B-line scores in the non-dry weight group reduced from 56.5 before to hemodialysis to 32 after hemodialysis.
In addition, lung ultrasonography is suggested as a method of measuring dry weight. Children's dry weight increases as they grow, while B-line scores remain unaltered. To determine a child's volume state, the number of B-lines in the dry weight state is useful [(6)].

It has also been advised to assess the level of hydration using cardiac biomarkers like BNP. Cardiomyocytes primarily in the heart ventricles produce these hormones in response to straining brought on by an increase in ventricular blood volume [(12)]. A key factor in the release of natriuretic peptides isoverhydration. It is unclear, according to some authors [(12,13)], whether these indicators represent fluid state or underlying organ structural damage.

Since the mean BNP before dialysis was 219.5±67.802 and the mean BNP after dialysis was 116.75±50.772, we noticed a trend of higher BNP readings in pre dialysis than post dialysis. Both the DWgroup (p<0.001) and the non-DW group (p<0.001) hadsignificantly lower BNP levels following dialysis. In comparison to the non-dry-weight group's mean BNP levels (284.3±40.9), the dry-weight group's mean BNP levels (184.6±51.7) were lower prior to dialysis. However, following dialysis, the dry-weight group's mean BNP levels were lower than those of the non-dry- weight group's (166.3±51.14), and this difference was statistically significant (p< 0.001).

According to our findings, LUS+ findings had higher BNP serum levels than LUS- findings. Afterdialysis, BNP levels for LUS- patients were88.69±22.845 pg/ ml while for LUS+ patients were 168.86±47.39 pg/ ml. Similar to this, **Giannese et al.** [(2)]demonstrated that BNP levels for LUS- patients were 74.2 pg/ml at the 25^{th} percentile and 137 pg/ml at the 75^{th} percentile, whereas BNP levels for LUS+ patients were 180 pg/ml at the 25^{th} percentile and 909 pg/ml at the 75^{th} percentile.

Our findings are represented by the ROC curve of BNP serum levels as a predictor of pulmonarycongestion. The curve's area under it was 0.967. According to the results, 100 pg/ml (sensitivity 100, specificity 92.3, positive predictive value 87.5, andnegative predictive value 100 with accuracy 95) is the ideal BNP cut-off value for predicting pulmonary congestion.

This shows that, in the absence of LUS, BNP levels may be a reliable proxy that can detect the existence of pulmonary congestion as found by anotherstudy [(2)].

In our study, in post-dialysis patients, BLScorrelated positively with BNP levels (r= 0.914, p < 0.001) with no significant correlation in pre-dialysis (r=0.276, p= 0.064). The same results were presented by **Giannese et al.** [(2)] **and Donadio et al.** [(14)]**,** who found that BNP and BLS had a positive correlation only whenBNP was measured after an HD session and not before.In contrast, **Basso et al.** [(15)] found no connection between BLS and BNP levels both before and after dialysis.
The systematic use of LUS in HD patients may be a beneficial clinical management technique for maintaining track of the dialysis population even when heart function is not impaired. Additional benefits for patients include the method's safety (compared to a chest X-ray or CT scan), repeatability, convenience of bedside deployment, and the clinical importance of the information it may give [(2)].

Unfortunately, a number of barriers prevent the LUS approach from becoming widely employed in ordinary clinical practice. Specifically, the availability of sonography, the operator's training and expertise, and the need for a longer hospital stay. One technique for expanding its use is to increase the possibility of LUS assessment at the patient's bedside and during or shortly after the end of the dialysis session. Overall, the implementation of LUS evaluation may be a realistic and secure tool for monitoring HD patients' fluid status.

Our study is open-minded for application ofLUS and serum BNP in optimizing dry weight, but we need for more studies with large sample size and serial LUS and BNP leveling.

CONCLUSIONS

According to our findings, numerous patients who were clinically euvolemic at the end of the HD session and assumed to be at goal dry weight developed lung congestion at LUS despite the absence of clinical indications of overhydration such as dyspnea, edema, and high blood pressure. This demonstrates that even if a patient achieves their purported target weight, they may still have residual volume overload, which a LUS scan can detect. When BLS exceeded 10, and BNP serum levels exceeded 100 pg/ml, lung congestion at LUS was expected. This means that BNP level can be used in the absence of LUS.

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