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The Diagnostic Value of Lung Ultrasound and Serum Level of Brain Natriuretic Peptide in Asymptomatic Pulmonary Congestion in Pediatric Hemodialysis Patients

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ABSTRACT
Background: Optimising the desired dry weight (DW) to reduce volume overflow in hemodialysis (HD) patients, depending on clinical evaluation, lacks accuracy as signs of hypervolemia are observed only when overhydration is significant.
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 volume overload in HD patient.
Patients and Methods: A prospective observational study was conducted on 20 HD pediatric patients with asymptomatic 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: Many patients who were considered to be at goal DW at the end of the HD session and who were clinically euvolemic with no clinical indications of overhydration, showed lung congestion at LUS. This suggests that even after a patient reaches their supposedly goal DW, they may still be experiencing a residual volume overload. If LUS cannot be used, BNP levelling may be able to help.
Keywords: Pulmonary congestion, LUS, BNP, HD, DW.

INTRODUCTION
Without hypovolemia or hypervolemia, DW is a volumetric condition. An accurate calculation of extravascular lung water is a key strategy to prevent these consequences since chronic hypovolemia and hypervolemia caused by erroneous DW estimation might result in chronic dehydration or long-term cardiovascular issues [(1)].

As shown by bioimpedance analysis (BIA), several patients who were clinically euvolemic and thought to be at target DW showed lung congestion at LUS in the absence of oedema, dyspnea, or overhydration [(2)].

LUS can assess the existence of pulmonary microcirculation congestion, which is common in HD patients but frequently asymptomatic and difficult to detect [(3)]. The air-water interface created by the increased pulmonary extravascular volume causes the echo detectable artefact known as the B line, and its identification enables the calculation of a BLS, which is used to measure pulmonary congestion [(4)].

Additionally, BNP serum levels may be helpful as a metric for excessive hydration; although its level is susceptible to a variety of influences, it may be interpreted as a measure of myocardial cell distension in response to circulating volume overload [(5)].

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

SUBJECTS AND METHODS
This prospective observational study was carried out from July 2021 to January 2023, in the Pediatric Nephrology Unit of the Benha University Hospital.
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 were included.

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 diseases such 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

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Homburg, Germany) at blood flow rate = 2.5 weight (kg) + 100 ml/min. The dialysis solutions contained bicarbonate.

The following procedures were applied to all patients:

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

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

Systemic examination, which included neurological, 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, and PTH.

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:

Benha Medical Ethics Committee of Benha Faculty of Medicine 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 parameters were 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 BNP were not significant.

Volume load parameters measured before and after dialysis:

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 mean decrease in weight, SBP and DBP were significant (Table 1).

Table (1): Volume load parameters before and after dialysis (n=20)

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 pressure after (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 patients and 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).

Table (2): Subgroup analysis of BNP and B line score by dry weight

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		

*: Significant

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 correlation in 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).

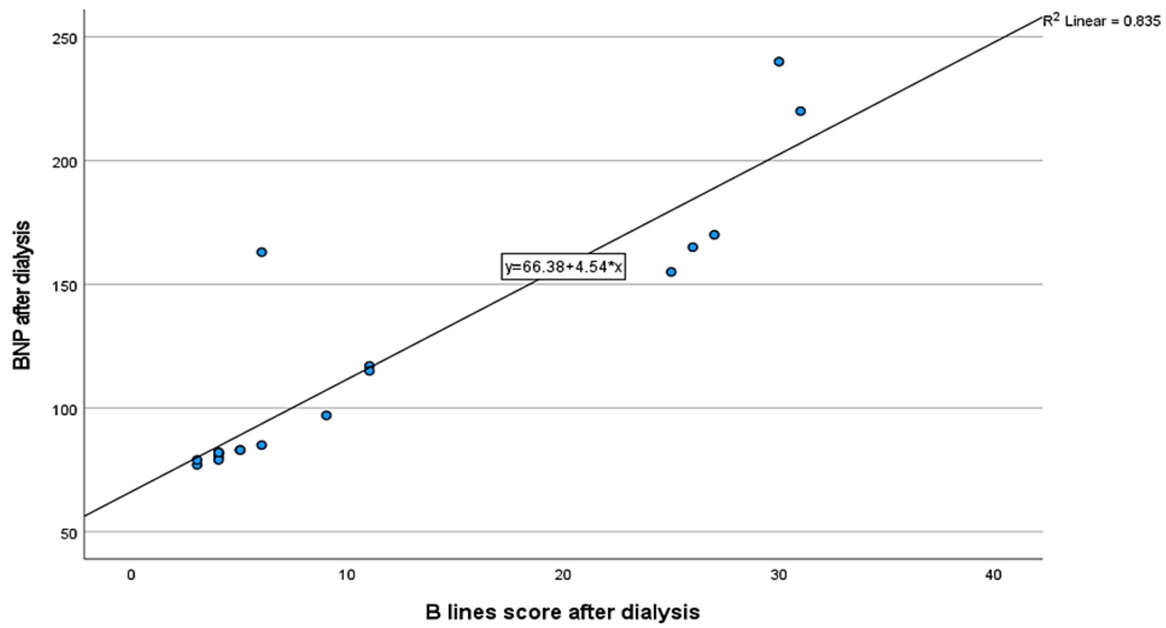

Figure (1): Showing that there was a substantial positive connection between the post-dialysis B-line score and the post-dialysis BNP.

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).

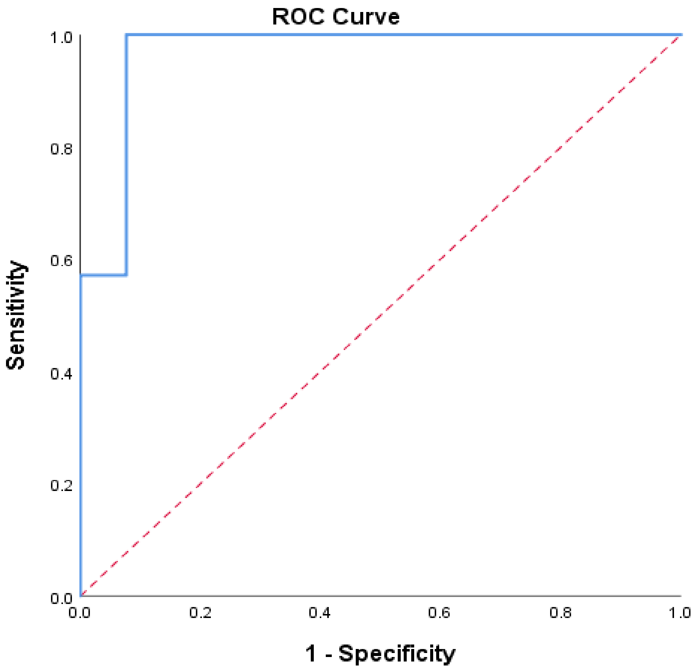

Figure (2): ROC curve of post-dialytic BNP for predicting pulmonary congestion.

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 according to BLS as BLS> 10 indicate pulmonary congestion.

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

Table (3): BNP levels in both dry and non-DW group according to pulmonary congestion finding (BLS> 10).

BNP (pg/ml)		**No pulmonary congestion (LUS-) (n = 13)**		**Pulmonary 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*
Dry weight, number (%)	Dry	12	92.3	3	42.9	0.031*
	Non	1	7.7	4	57.1	

*: Significant

DISCUSSION

At the patient's bedside, a clinical examination is the traditional method for determining their level of hydration. It may, however, be criticised on a more detailed level. Both a gold standard to determine the DW and a validated clinical score to evaluate hydration status in HD patients are presently lacking [(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/ml at the end of the HD session, without any signs of edema, dyspnea, or high blood pressure. Three patients also attained their reported dry weight.

This finding is consistent with information from other studies, such as the one by **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 expert pediatric cardiologist, 14 patients had normal Echo findings and 6 patients revealed LVH.

Our results showed no difference as regard BLS and BNP in both LVH and non LVH group. Similar to this, **Mouche *et al.*** [(10)] demonstrated that there were no appreciable variations between patients with or without LVH and pre-HD BNP levels. Also**, Giannese *et al.*** [(2)] demonstrated that there is no difference between LUS+ and LUS- individuals when cardiac pathology, such as LVH, is taken into account. In contrast, **Vaičiūnienė *et al.*** [(11)] found that the results of the BIA test the LVH patients were dehydrated. Before HD, patients with LVH had much more B lines on lung US, and both before and after HD, their BNP levels were more than three times higher. Both before and after HD, LVH patients had greater SBP.

In terms of mean B-line scores, there was a highly 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-weight group were lower before dialysis (12.7± 3.8) than those of 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 after dialysis (22.7 ± 8.96), and this difference was statistically significant (p< 0.001).

These findings corroborated those of **Fu *et al.*** [(6)]**,** who found that in the dry weight group, mean B-line scores decreased from 23.5 prior to hemodialysis to 8.5 afterwards. Mean B-line scores in the non-dry weight group decreased from 56.5 before to hemodialysis to 32 following hemodialysis.

In addition, lung ultrasound is suggested to be a measure of dry weight. Children's dry weight rises as they grow, but B-line scores are unaffected. For determining 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 is overhydration. 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 DW group (p<0.001) and the non-DW group (p<0.001) had significantly 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. After dialysis, BNP levels for LUS- patients were 88.69±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 25th percentile and 137 pg/ml at the 75th percentile, whereas BNP levels for LUS+ patients were 180 pg/ml at the 25th percentile and 909 pg/ml at the 75th percentile.

Our findings are represented by the ROC curve of BNP serum levels as a predictor of pulmonary congestion. 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, and negative 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 another study [2].

In our study, in post-dialysis patients, BLS correlated 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 when BNP 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 useful clinical management tool for keeping track of the dialysis population even when heart function is not compromised. The method's safety (in comparison to a chest X-ray or CT scan), repeatability, convenience of bedside deployment, and the clinical significance of the information it may provide are additional advantages for patients [2].

Unfortunately, a number of obstacles prohibit the LUS method from being widely used in routine clinical practise. Specifically, the availability of sonography, the operator's training and experience, and the demand for a lengthier hospital stay. One strategy to broaden its use is to improve the likelihood of LUS assessment at the patient's bedside and during or soon following the conclusion of the dialysis session. Overall, the application of LUS evaluation may be a practical and secure method for monitoring HD patients' fluid status.

Our study is open-minded for application of LUS 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 results, several patients who were clinically euvolemic at the conclusion of the HD session and thought to be at goal dry weight showed lung congestion at LUS in the absence of clinical signs of overhydration such dyspnea, edema, and high blood pressure. This shows that even when a patient reaches their alleged target weight, they may still have a residual volume overload that LUS examination can detect. When BLS > 10, and BNP serum level > 100 pg/ml, lung congestion at LUS was predicted. This implies that BNP level may be employed in the absence of LUS.

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