The Role of Chest Ultrasound Combined with Plasma Brain Natriuretic Peptide in The Differentiation between Cardiogenic and Noncardiogenic Pulmonary Edema

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ABSTRACT
Background: Pulmonary edema is a medical emergency that threatens life, and requires urgent management and immediate hospitalization. Since there is no definite "gold standard" for diagnosing ALI/ARDS or cardiogenic pulmonary edema (CPE), there is no technique or known biomarker that can be used to distinguish between the two conditions. Combining clinical criteria with other proven diagnostic methods, such as BNP and chest ultrasonography, can increase the predicted accuracy, assist in therapy, and enhance the results.
Objective: The purpose of this study is to assess how well plasma brain natriuretic peptide (BNP) and chest ultrasonography can distinguish between cardiogenic and noncardiogenic pulmonary edema.
Patients and methods: Lung US was applied to respiratory distressed patients In Benha University Hospital Chest ICU and Emergency Department on 50 subjects through a cross-sectional prospective study. They were divided into CPE group 20 cases) and NCPE group (20 cases) as well as the control group (10 cases). Alveolar-interstitial syndrome (AIS), absence or decreased lung sliding, sparing regions, subpleural consolidation, pleural line abnormalities, and pleural effusion were among the pleuropulmonary symptoms that were targeted for detection by the LUS scan in both groups. Plasma BNP levels were assessed in all groups.
Results: Consolidation is another sonographic finding in the Non-CPE group which represents 80% of cases and is present in 5% only in the CPE group in our study. Pleural effusion is not a specific finding between the two groups but it was higher among the cardiogenic group representing 65% while was 25% only among the non-cardiogenic group. BNP was significantly higher in the CPE group (1031 pg/ml) than in the Non-CPE group (346.5 pg/ml) and controls (63.5 pg/ml) (P <0.0001). BNP was valid for differentiation between CPE and non-CPE with a Cutoff point of >740 pg/ml (70% Sensitivity and 100% Specificity).
Conclusion: CUS in combination with BNP represents a useful tool for differentiating CPE from non-CPE. In emergency settings, the benefits of their use outweigh the presence of limitations.
Keywords: CPE, non-CPE, Lung ultrasonography, Chest ultrasound, Brain natriuretic peptides.

INTRODUCTION
Pulmonary edema is a health emergency that threatens life and needs urgent management and immediate hospitalization [(1)].

It happens when one or more of Starling's forces change, which causes more fluid to migrate into the alveoli. High pulmonary capillary pressure is what causes the aberrant fluid flow in cardiogenic pulmonary edema. Contrarily, noncardiogenic pulmonary edema is brought on by many diseases in which alveolar protein and fluid buildup are due to causes other than increased pulmonary capillary pressure [(2)].

History, signs, and symptoms may be enough to determine the origin of edema clinically, but in many other situations, particularly in a critical care scenario, the distinction between cardiogenic and noncardiogenic causes may be difficult. Because different treatments are available depending on the underlying pathophysiologic mechanisms, the diagnosis is crucial [(3)]. Brain Natriuretic Peptide (BNP) was the most often examined serum and pulmonary biomarker used to distinguish ALI/ARDS from CPE [(4)].

BNP is released from the cardiac ventricles in response to an increase in heart wall tension. Rapid measurement of BNP is a sensitive indicator of dyspnea and hypoxemic respiratory failure brought on by cardiac reasons in the emergency room and intensive care unit. Therefore, in these conditions, it might be the most useful for excluding CPE [(5)].

Transthoracic ultrasound is an easy, bedside, low-cost, and lacks radiation tool that has proved its worth as a strategic instrument to be used directly after the clinical investigation in the emergency room, intensive care unit, operating room, and clinical routine [(6)]. It has developed into an important point-of-care (POC) tool for the evaluation of a range of pulmonary and pleural disease states, including pleural effusion, empyema, pneumonia, pneumothorax, lung cancer, and pulmonary embolism [(7)].

Since there is no definite "gold standard" for diagnosing ALI/ARDS or CPE, there is no technique or known biomarker that can be used to distinguish between the two conditions. Combining relevant biomarkers with clinical criteria and other techniques may increase the prediction power, facilitate the management, and enhance results [(4)].

The purpose of this study was to assess the contribution of plasma brain natriuretic peptide (BNP) and chest ultrasonography to the distinction between cardiogenic and noncardiogenic pulmonary edema.

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PATIENTS AND METHODS

This cross-sectional prospective study was carried out in the Respiratory Intensive Care Unit and Emergency Department at Benha University Hospital in the period between August 2019 till February 2022. Patients were eligible for participation in this study as follows: CPE group diagnosed based on clinical signs and symptoms, echocardiography, and chest radiography with the following features: Mediastinal widening as shown by an expansion of vascular pedicles (>53 mm). If present, pleural effusion Cardiomegaly. Cuffing of the peribronchium. The presence of bronchovascular markings is a sign of upper lobe pulmonary venous diversion. thickened septal lines and Kerley's B lines. pulmonary opacities affecting both the central (primarily) and peripheral lungs. a smaller lung capacity.

NCPE diagnosis based on "Berlin definition"[8]: (1) Beginning one week after a recognized clinical insult or after the onset of new or worsening respiratory symptoms. (2) Bilateral opacities on a chest X-ray that are not entirely explained by an effusion, a collapsed lung, or nodules (3) The diagnosis of respiratory failure when heart failure or fluid overload cannot adequately account for it. (4) The presence of hypoxemia, as defined by a specified threshold of the PaO2/FiO2 ratio assessed with a minimum need of PEEP 5 cm HO, identifies three severity categories: Mild (200 mm Hg < PaO2/FiO2 ≤ 300 mm Hg), Moderate (100 mm Hg < PaO2 /FiO2 ≤ 200 mm Hg), Severe (PaO2 /FiO2 ≤ 100 mm Hg).

On admission and after being diagnosed using clinical and radiological data, LUS was used.

Curvilinear array 4 to 5 MHz transducer, is considered the best chest ultrasound probe that facilitates examination of a patient unable to cooperate by sitting which is important for imaging deeper chest structure Micro convex probes are directly applied to the intercostal space. A linear array 6 to 12 MHz transducer, is used to visualize superficial structures such as pleural thickening, pneumothorax, pleural masses, or subpleural parenchymal lesions of the lung.

The examination was done next to the patient's bed. The posterior thorax was scanned while sitting or in a lateral posture. A lateral decubitus posture was utilized to investigate the posterior lung areas of individuals in whom the sitting position could not be employed.

A probe is placed vertically along both sides of each intercostal space (the parasternal line, anterior axillary line, and posterior axillary line). Data were shown on a screen. Five zones should be established for each hemithorax: two anterior, two lateral, and one posterior. The third intercostal gap should be present between these zones.

The following ultrasonographic signs were investigated in this study to differentiate between CPE and NCPE [9]:

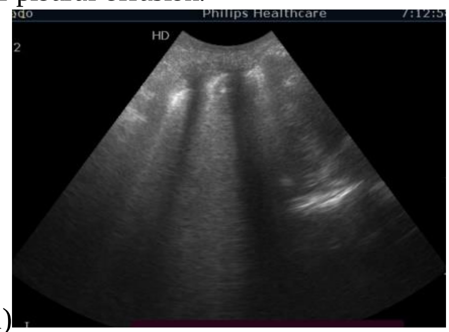
- Alveolointerstitial syndrome (AIS) is characterized by the presence of a "white lung" or more than three ultrasound lung comets (B lines) in each studied location.
- As evidence of pleural movement, pleural line sliding precludes pneumothorax, which may be absent or diminished with acute lung damage, lobar consolidation, and atelectasis. It also suggests a pulmonary region in touch with the thoracic wall. Pleural line abnormalities were characterized as thickening larger than 2mm, proof of minor subpleural consolidations, or a coarse look of the pleural line; their existence suggests a process of either consolidation or enlargement (APE).
- A pleural effusion that manifested as diaphragm-bound anechoic zones.
- Spared areas are normal areas of the lung surrounded by areas of AIS.
- Subpleural consolidation, Air bronchogram which appear mainly in cases of NCPE appear as comet tail appearance.

2.5-4 ml of blood were withdrawn from each case, two ml of blood were obtained and were immediately placed into plastic collection tubes containing ethylenediaminetetraacetic acid sodium 9 (EDTA) as an anticoagulant, and centrifuged at 3000 rpm for 10 minutes at 4oc. The supernatant was collected to avoid hemolysis. Sample aliquots were stored at -20°C or -80°C with the avoidance of repeated freeze-thaw cycles till the time of assay using the enzyme-linked immunosorbent assay (ELISA) [10].

(a) 

(b) 

Figure (1): Ultrasound findings in a patient presented with acute CPE showing a) Homogenous AIS (B lines), no pleural line abnormalities, and no consolidations were present. b) Showing the presence of a moderate amount of pleural effusion.

(a) 

(b) 

Figure (2): Ultrasound findings in a patient presented with Non- CPE a) Showing AIS, pleural line thickening, and irregularities. Consolidation is present. b) Showing presence of consolidation and pleural effusion.

Ethical consent:

The academic and ethical committee of Benha University granted its clearance for the project. All study participants provided written informed permission after being informed of our research's goals. The Declaration of Helsinki for human beings, which is the international medical association's code of ethics, was followed during the conduct of this study.

Statistical Methods

Data were gathered, updated, then in an excel file, extracted, and programmed. The Statistical Package for Social Science (SPSS) version 26 was used to examine the coded data. With the help of the mean ±Standard Deviation (SD) for continuous variables and frequency and percentage for categorical variables, the examined data was shown in the appropriate tables and graphs. The Chi-Square test was used to look at the association between two qualitative variables, while the independent 2 samples t-test was used to investigate differences in continuous data between the independent two groups.

When the Chi-square test assumptions were broken (the predicted count is less than 5 in more than 20% of cells), Fisher's exact test was employed to investigate the association between two qualitative variables. The following indicators were generated to gauge how well US parameters may predict naturally occurring pulmonary edema and to compare them: Sensitivity, specificity, accuracy, and the likelihood of a good or negative outcome. Each parameter also had a receiver operating characteristic (ROC) curve created for it, and the statistical differences between the ROC curves' areas under them and 0.5 were computed as well as checked for significance. The 0.05 threshold of significance was used for all tests of significance.

RESULTS

This study was carried out on 50 subjects at the Chest Department ICU and emergency department at Benha University Hospital. They were classified into three groups: CPE group: 20 patients presented with acute dyspnea with a provisional diagnosis of cardiogenic pulmonary edema (CPE).

Non-CPE group: 20 patients presented with acute dyspnea with a provisional diagnosis of noncardiogenic pulmonary edema (Non-CPE).

Controls: 10 apparently healthy subjects as a control group.

Table (1): Basic characters in all studied groups

Basic characters		CPE group (n=20)		Non-CPE group (n=20)		Controls (n=10)		ANOVA/X2	P
		Mean / n	SD / %	Mean / n	SD / %	Mean / n	SD / %		
Age		60.7	6.76	50.55	11.83	54.00	10.53	5.455	0.072
Sex	Male	12	60	10	50	6	60	0.487	0.784
	Female	8	40	10	50	4	40		
Smoking	Current smoker	10	50.0	6	30.0	2	20.0	4.231	0.376
	Non-smoker	7	35.0	12	60.0	7	70.0		
	Ex-smoker	3	15.0	2	10.0	1	10.0		

COVID Pneumonia was the main cause of admission in the non-CPE group (65%) followed by aspiration and extrapulmonary sepsis (15%) for each of them (**Table 2**).

Table (2): Causes of admission in the Non-CPE group

	Non-CPE group (n=20)	
	n	%
COVID pneumonia	13	65.0
Aspiration	3	15.0
Extrapulmonary sepsis	3	15.0
Near drowning	1	5.0

Regarding US findings, there was a statistically significant difference between CPE and NCPE regarding pleural line abnormalities, consolidation, spared areas, and impaired or absent pleural sliding (P>0.0001). No statistically significant difference was found regarding AIS (P =1) or evidence of pleural effusion (P 0.028).

AIS was detected in all patients of CPE and Non-CPE groups (100%). which provides the main sign of pulmonary edema either in the cardiogenic group or non-cardiogenic one. Spared areas is a highly specific finding in Non-CPE cases that is present in (100%) of patients of this group and absent in the CPE group which is characterized by a homogenous pattern. Pleural line abnormalities are important sonographic signs which present in (100%) of patients in the Non-CPE group and 10% of the CPE group in our study. Impaired or absence of lung sliding is considered a highly significant US finding which was present in (75%) of cases in the Non-CPE group and absent in the CPE group. Consolidation is another sonographic finding in the Non-CPE group which represents 80% of cases and is present in 5% only in the CPE group in our study. Pleural effusion is not a specific finding between the two groups but it was higher among the cardiogenic group representing 65% while was 25% only among the non-cardiogenic group.

On basis of sensitivity and specificity of US parameters in differentiation between CPE and Non-CPE, ultrasound parameters including five signs were significantly different between CPE and Non-CPE groups, and each one could be used as an independent parameter given its sensitivity and specificity (**Table 3).**

Table (3): US finding in CPE and Non-CPE groups

		CPE group (n=20)		Non-CPE group (n=20)		X2	p
		n	%	n	%		
AIS	No	0	0	0	0	40	1
	Yes	20	100	20	100		
Thickened irregular pleural line	No	18	90	0	0	32.73	<0.0001
	Yes	2	10	20	100		
Consolidation	No	19	95	2	20	36.19	<0.0001
	Yes	1	5	18	80		
Spared areas	No	20	100	0	0	40.00	<0.0001
	Yes	0	0	20	100		
Evidence of pleural effusion	No	7	35	14	70	14.9	0.028
	Yes	13	65	6	30		
Impaired or absent pleural sliding	No	20	100	5	25	24.00	<0.0001
	Yes	0	0	15	75		

BNP was significantly higher in the CPE group (1031 pg/ml) than in the Non-CPE group (346.5 pg/ml) and controls (63.5 pg/ml) (P <0.0001) (**Table 4**).

Table (4): Serum BNP in all studied group

	CPE group (n=20)		Non-CPE group (n=20)		Controls (n=10)		Anova	P
	Mean	SD	Mean	SD	Mean	SD		
Serum BNP(Pg/ml)	1031	254.31	346.5	84.45	63.500	11.316	27.281	<0.0001

BNP was valid for differentiation between CPE and non-CPE with a Cutoff point of >740 pg/ml (70% Sensitivity and 100% Specificity) **(Table 5**).

Table (5): Validity of BNP in differentiation between CPE and NCPE

The area under the ROC curve (AUC)	0.880
Cutoff point	>740
P value	<0.0001
Sensitivity	65.00
Specificity	100.00

DISCUSSION

Acute dyspnea is a common reason for admission to emergency departments (ED). One of the clinical and paraclinical parameters that can help clinicians is the capacity to discriminate between cardiac and pulmonary causes of acute respiratory distress. The patient's history, physical examination, and bedside ultrasonography are examples of these measures. Some have put diagnostic criteria in place, such as the Framingham Heart Failure Guidelines. Acute respiratory distress due to cardiogenic causes can be ruled out or identified by utilizing brain natriuretic peptide (BNP) or the N-terminal of the pro-hormone brain natriuretic peptide (BNP) (NT-pro-BNP) [(11)]. However, some ailments, such as renal failure, critical sickness, pulmonary heart disease, arrhythmia, anemia, valvular heart abnormalities, and muscular diseases, may influence BNP values [(9)].

Lung ultrasound (LUS) imaging research, a novel imaging technology, has been investigated in recent years and has shown promising results for diagnosing AHF at an early stage. With strong sensitivity and specificity, LUS can detect interstitial pulmonary syndrome by looking for a "so-called" comet tail artifact. This is a useful tool that may be used at the bedside in the ED, is simple to use and understand, and can be repeated over time [(12)]. The following signs of CPE or non-CPE pulmonary edema can be distinguished by the US to aid in the ultimate diagnosis of pulmonary edema incidence in diseased groups of patients: Finding the existence of the two groups was the main goal of the ultrasound examination. 1) Alveolar-interstitial syndrome (AIS), 2) Anomalies of the pleural lining, 3) "spared regions", 4) "gliding" sign being absent or reduced, 5) consolidations, 6) Pleural effusion and 7) "lung pulse." [(13)].

It has been claimed that AIS on an ultrasonogram is an indication of pulmonary edema in both ARDS and APE patients. All of the patients in the current study's CPE and CPE groups displayed AIS or a diffuse B-line profile. This is consistent with the research by **Copetti *et al.*** [(9)]**,** which examined 58 patients who met the criteria for either ALI/ARDS (18 instances) or APE (40 cases), and found that all of the patients had diffuse B lines.

Similar results were reported by **Zanobetti *et al.*** [(14)], who discovered that diffuse AIS, which is frequently a symptom of APE, has a diffuse B-line profile, which is its distinctive ultrasonographic pattern. Additionally, this concurs with research by **Daabis *et al.*** [(15)]**,** which looked at 100 ICU patients who had acute respiratory failure. Ten instances involved ARDS. For determining the cause of acute respiratory failure, they contrasted CUS with the available diagnostic techniques. In every instance of ARDS, the typical ultrasonography B profile was discovered. Similar results were discovered in the **El-Naggar *et al.*** [(16)] investigation.

Spared areas are a highly specific finding in NCPE cases and not present in the CPE group which is characterized by a homogenous pattern. In this study, spared areas were found in 100% of the Non-CPE group while the non-CPE group showed any spared areas. In agreement with **Copetti *et al.*** [(9)] on 58 patients, "Spared regions" were observed in 100% of ALI/ARDS patients and 0% of APE patients (p <0.0001).

Pleural line abnormalities are important sonographic signs which present in all patients of the non-cardiogenic group (100%) in our study and 2 patients (10%) of the cardiogenic group. Since pleural line anomalies were seen in all patients with ALI/ARDS and 25% of patients with APE (p <0.0001), these findings were equivalent to those of the **Copetti *et al.*** [9] research of the same subject population. **El-Naggar *et al.*** [16] found anomalies in the pleural line in all patients with ALI/ARDS and none of the patients with APE.

Impaired or absence of lung sliding is considered a highly significant US finding which was detected in 75% of the NCPE group and not present in the CPE group of our study. **El-Naggar *et al.*** [16] found a reduction or absence of pleural sliding in all ARDS patients in their study. Additionally, **Copetti *et al.*** [9] found that 100% of patients with ALI/ARDS and 0% of patients with APE had the "gliding sign" absent or reduced.

Consolidation is another sonographic finding in the non-cardiogenic group which represents 80% of cases and in 5% only of patients with CPE in our study. These results were similar to those of El-**Naggar *et al.*** [16] who discovered that lung consolidation was present in 93.3% of cases of ARDS but not in any cases of APE (0%) or **Copetti *et al.*** [9] who discovered that lung consolidation was present in 83.3% of cases of ARDS but not in cases of APE. Also, our results are comparable with **Sanjan *et al.*** [17] on 73 respiratory distressed patients who found that consolidation was present in moderate (100%) and severe (92.3%) ARDS.

Pleural effusion is not a specific finding between the two groups in this study, it was higher among the cardiogenic group representing 65% while was 30% among the non-cardiogenic group. In **El-Naggar *et al.*** [16] study, more frequently, pleural effusions were observed in 76% of the CPE group and 40% of the ARDS group of patients. **Copetti *et al.*** [9] reported similar outcomes. As a result, their existence cannot be used for differential diagnosis alone.

Results of our study are also comparable to **Kasem *et al.*** [18] study based on chest ultrasound pleural line abnormalities, absence of lung sliding, and spared area in all patients with ARDS while consolidation and pleural effusion presented in 29(83.3%) and 21(60%) patients with ARDS, respectively. While consolidation and pleural effusion presented in 1(4%) and 23(29%) patients with CPE, respectively.

On basis of sensitivity and specificity of US parameters in differentiation between CPE and Non-CPE, in presence of AIS, our results showed that the detection of thickened irregular pleural lines, consolidation, spared areas, impaired or absent pleural sliding are strongly predictive for Non-CPE.

This study showed that spared areas had the highest accuracy (100%) followed by pleural line abnormalities (95%) then consolidation (92.5%) and impaired lung sliding (87.5%). These results are comparable to **El-Naggar *et al.*** [16] study, the accuracy for absent or reduced pleural sliding and consolidation in cases of ARDS in pleural line anomalies was 100%, 100%, and 92.8 %, respectively. Also, these results match **Copetti *et al.*** [9] study, where accuracy for spared areas (100%), impaired lung sliding (100%), consolidation (92.5%), and pleural line abnormalities were (72.5%).

In this study, BNP was significantly higher in the CPE group (1031 pg/ml) than Non-CPE group (346.5 pg/ml) and controls (63.5 pg/ml) (P <0.0001), similar to the **Ray *et al.*** [19] research, which comprised 200 patients with a mean age of 80; 88 of them (44%) developed CPE. Since the median BNP was much greater in the group of CPE, there was a significant link between the BNP readings.

Additionally, the initial plasma BNP levels of the patients with CPE and ALI/ARDS were noticeably different in the study by **Komiya *et al.*** [4]. The area under the ROC curve was 0.83 (p 0.001). A BNP threshold value of 500 pg/mL demonstrated a sensitivity of 69.0%, specificity of 83.1%, and accuracy of 75.0% for detecting CPE, which is in agreement with our findings.

CONCLUSION

CUS in combination with BNP represents a useful tool for differentiating CPE from non-CPE. In emergency settings, the benefits of their use outweigh the presence of limitations.

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