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Letter to the Editor

Phenotyping pleural effusion in patients hospitalized in Internal Medicine wards with decompensated heart failure☆

Dear Editor,

Acute decompensation of heart failure (ADHF) is the most common reason for hospitalization in patients above the age of 65 years in Western countries [1]. Congestion represents a key clinical feature in heart failure, as most hospitalizations for acute decompensation are related to fluid overload or redistribution rather than to low cardiac output [2].

Pleural effusion (PE) is one of the main signs of congestion evaluated by the clinician. PE in patients with congestive heart failure is typically bilateral. When unilateral, different studies reported a higher prevalence of right-sided PE [2]. Furthermore, in everyday clinical practice, the distribution of PE is frequently employed as a criterion for differential diagnosis retaining possible ADHF diagnosis in case of bilateral or -secondary- in right sided PE. Nevertheless, conclusive data about the distribution of PE and its aetiological relationship are lacking and still debated.

As for pulmonary congestion, PE can be accurately detected by lung ultrasound (LUS). Depending on the imaging method and the study setting, the reported prevalence of PE in ADHF varies considerably, ranging from 47 % to 89 % [1]. The high variability in the prevalence of PE could be related to the low sensitivity of X-ray, still used as a diagnostic method in many studies [3].

Some hypotheses about the prevalence of right-sided PE in unilateral effusion have been postulated, all concerning anatomical issues like the compression of right pulmonary veins due to right atrial dilatation, yet today neither of these has been universally accepted [2].

Overall, the pathogenesis of PE in heart failure is multifactorial and poorly characterized. Different studies tried to correlate the PE presence with different parameters including systolic or diastolic heart function. Diastolic dysfunction seems to play a role in PE formation rather than systolic dysfunction.

However, only a few studies are available, and they are carried out in very specific patient settings (e.g. young patients with severe diastolic dysfunction, heterogeneous imaging evaluation) [4,5].

Moreover, to the best of our knowledge, the prognostic role of residual PE at discharge has been poorly investigated. At this regard, the simplicity of ultrasound PE detection could make this variable highly informative, even considering that the most accurate method for evaluating B-lines is still matter of discussion [6].

The aim of our study was to describe the characteristics of PE detected by lung ultrasound (LUS) in patients hospitalized for decompensated heart failure in Internal Medicine wards.

In particular, we investigated:

- The prevalence and the distribution of PE at admission and discharge.
- The correlation between PE and echocardiographic signs of systolic and diastolic function.
- The prognostic role of residual PE at discharge.

This study represents a sub-analysis of the previously published multicentric DRY-OFF study [7]. Briefly, 314 consecutive patients admitted to Internal Medicine departments for ADHF from October 2018 to February 2020 were prospectively enrolled. The diagnosis of ADHF was formulated according to the European Society of Cardiology [1].

Exclusion criteria were: age <18 years; pregnancy; acute coronary syndromes; creatinine clearance <30 mL/min or dialysis; recent (<3 months) pneumonia; ongoing sepsis; interstitial lung disease; massive PE; chronic liver disease; bedridden condition; any concomitant cancer; hemodynamic instability.

In the emergency department, each patient had a chest X-ray. At the time of ward admission, LUS was performed to assess the presence and severity of PE. The LUS was then repeated at discharge. LUS was performed at bedside with the patient in a seated position, using a convex probe (3.5–5 MHz, lung preset) to identify and quantify PE and B-score, the scoring method used in the original DRY-OFF study to quantify the pulmonary congestion [7].

We performed a semiquantitative evaluation of the PE:

- Mild: single longitudinal ultrasonography scan
- Moderate: two longitudinal ultrasonography scans
- Severe: three or more longitudinal ultrasonography scans.

During the hospital stay, a complete 2D Color-doppler echocardiography was performed by an experienced operator according to the American Society of Echocardiography guidelines [8].

NT-pro-BNP was measured in all patients at the time of admission and discharge.

90-days death and re-hospitalization were recorded to evaluate patients' short-term prognosis.

Regarding statistical analysis, data were expressed as mean ± standard deviation or as absolute frequency and percentage, as appropriate. Between groups comparisons were performed by Chi Square test or

☆ Ethics statement: All the data were anonymized. The Institutional Review Board of our University Hospital (Luigi Sacco Hospital, University of Milan, Italy) approved the study protocol. The study was carried out in compliance with the ethical principles of the Declaration of Helsinki (with amendments) and Good Clinical Practice.Funding: none.Declaration of Competing Interest: the authors have no conflicts of interest.

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independent T-test. P-value less than 0.05 was considered statistically significant.

All calculations were made by using SPSS for Windows Version 22; Excel – Office 2016. The study protocol complied with the Declaration of Helsinki and was approved by the ethics committee of each participating Institution (protocol number of the coordinating center 473/2018). Written informed consent was obtained for all study participants.

A total of 314 patients (mean age 81.8 ± 8.6 years) with decompensated heart failure were included in the study. Most of the patients had a previous history and previous hospitalization for congestive heart failure. Study population characteristics are fully described in the original article. [7] At admission the prevalence of PE was 67.5 % among all patients, with a significantly higher prevalence of bilateral pleural effusion (BPE) (53.6 % BPE vs 15.6 % unilateral pleural effusion, UPE, $p < 0.01$). However, among patients with bilateral PE, a higher prevalence of larger PE on the right side than on the left side was detected (Table 1). At admission, no significant statistical difference was found between unilateral right-sided or unilateral left-sided PE, while at discharge unilateral right side PE were more frequent (11.8 % UPE right vs 5.7 % UPE left, $p = 0.03$).

PE was found in 181 patients by X-ray and 212 by ultrasound, confirming the greater sensitivity of the latter in the diagnosis of PE.

Echocardiographic parameters, inferior vena cava (IVC) diameters and B lines were evaluated comparing patients with and without PE at admission.

Patients with PE had a statistically significant higher B-score and IVC diameters (B-score 0,73 in patients without PE vs 0,85 in patients with PE, $p = 0{,}025$; expiratory IVC 19,34 mm vs 21,33 $p = 0{,}003$; inspiratory IVC 13,68 vs 16,39 $p = 0{,}001$). No statistically significant differences were observed in diastolic and systolic parameters (Table 2).

We found statistically significant higher values of NT-pro-BNP at admission in patients with PE (10,174,8 ± 12,742,1 ng/l in patients with PE vs 5303,6 ± 7535,3 ng/l in patients without PE; $p = 0{,}009$).

302 patients completed the 90-days follow up, of them 89 had an event (56 patients required hospitalization and 33 died). The presence of residual PE of any size at discharge was significantly associated with a worse prognosis at 90 days (Table 2).

A better understanding of the PE distribution is clinically relevant given the high prevalence of ADHF presenting with this clinical feature [1]. While literature agrees on the higher prevalence of bilateral PE in ADHF, no conclusive data exist on the distribution of unilateral PE. Historically, heart failure was associated with right UPE [2] whereas in our study it appears that the difference between unilateral right and left PE doesn't seem to be statistically significant. Therefore, the finding of a left UPE at admission should not a priori exclude the diagnosis of ADHF.

As expected, the presence of PE correlated to parameters of congestion such as B-score, IVC diameters and NT-pro-BNP values.

Our study did not show a statistically significant correlation between the presence of PE and echocardiographic parameters of diastolic and systolic function. While data on systolic function agree with the literature, some studies have shown a correlation between PE and altered E/A ratio. Nevertheless, these cited studies analysed a selected population: young patients without significant comorbidities, high prevalence of severe diastolic dysfunction ($E/A > 1{,}8$; $E/e' > 18$), sinus rythm [4,5]. In our population the high prevalence of atrial fibrillation (55 %) have limited E/A acquisition. On the other hand, it is possible that the high prevalence of diastolic dysfunction in our older and more comorbid population makes these parameters poorly specific in this context.

Yoku H. et al. found that the cumulative 1-year incidence of death and hospitalization was significantly higher in the residual PE group than in the no PE group [9]. For the first time our study investigates the role of PE at discharge in the short-term prognosis, showing an association between 90-days outcome and residual PE. Our finding is in line with other studies that evaluated the role of residual congestion, in term of lung B-lines and IVC plethora evaluated by ultrasound [10]. This evidence is particularly important taking into consideration that the detection of PE is one of the simplest, faster, and more accurate application of ultrasound, either in the hands of physicians or nurses [11].

This study has the limitation that we have excluded patients with massive PE at admission. This choice was taken because the presence of severe PE could have affected the B-lines evaluation in the original study. However, it must be pointed out that from the literature less than 2 % of patients with massive effusion eventually reach a diagnosis of heart failure [12].

In conclusion, our study highlights that the distribution of PE does not preclude the diagnosis of ADHF, being unilateral and left-side PE present in a non-trivial percentage of patients. Although these data should be confirmed by larger studies, the presence of PE would not appear to correlate with either diastolic or systolic function parameters, but only with other indicators of congestion (IVC index and B-score). Being a simple, accurate and fast evaluation, residual PE should be taken into account in the short-term prognosis estimation as a part of pre-discharge congestion assessment.

Table 1
Characteristics of the pleural effusion detected by ultrasound on admission and discharge. In bold: significant p values.

		Total population	
		n. (%)	P
ADMISSION	Pleural effusion	212 (67,5 %)	
	Bilateral pleural effusion	167 (53,2 %)	**< 0,01**
	Unilateral pleural effusion	45 (14,3 %)	
	Bilateral PE, > left	14 (8,4 %)	**0,02**
	Bilateral PE, > right	31 (18,6 %)	
	Unilateral left PE	16 (5,1 %)	0,07
	Unilateral right PE	29 (9,24 %)	
DISCHARGE	Pleural effusion	125 (39,8 %)	
	Bilateral pleural effusion	70 (22,3 %)	0,273
	Unilateral pleural effusion	55 (17,5 %)	
	Unilateral left PE	18 (5,7 %)	**0,03**
	Unilateral right PE	37 (11,8 %)	

PE: pleural effusion.

Table 2
Ultrasonography and ECG characteristics and 90-days prognosis in patients with and without pleural effusion at admission.

		No pleural effusion mean ± SD/ n. (%)	Pleural effusion mean ± SD/ n. (%)	p-value
Ecocardiography	AF	53 (52 %)	124 (58,5 %)	0,274
	EF (%)	48,4 ± 11,9	45,6 ± 13,6	0,073
	RV base (mm)	38,6 ± 9,1	38,8 ± 8,8	0,875
	TAPSE (mm)	18,5 ± 13,4	16,9 ± 5,1	0,184
	PASP (mmHg)	42,6 ± 13,9	39,5 ± 14,6	0,137
	TR (at least moderate)	35 (34,3 %)	78 (36,8 %)	0,668
	E/A	1,2 ± 0,7	1,3 ± 0,9	0,338
	E/e'	12,9 ± 4,9	14,1 ± 6,5	0,148
	TAPSE/PASP	0,54 ± 0,9	0,48 ± 0,3	0,421
Congestion	B-score	0,73 ± 0,4	0,85 ± 0,4	**0,025**
	IVC exp	19,3 ± 5,2	21,3 ± 5,3	**0,003**
	IVC ins	13,7 ± 6,5	16,4 ± 6,0	**0,001**
	NT-pro-BNP (ng/l)	5303,6 ± 7535,3	10,174,9 ± 12,742,1	**0,009**
F.U.	Hospitalization or death	44 (23,6 %)*	45 (38,8 %)*	**0,005**

In bold: significant p values.
AF: atrial fibrillation; EF: ejection fraction; RV base: right ventricular base; TAPSE: tricuspidal annulus plane systolic excursion; PASP: pulmonary artery systolic pressure; TR: tricuspidal regurgitation; IVC: inferior vena cava; exp: expiratory; ins: inspiratory.
* only 302 patients have completed 90-days follow up.

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