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Heart diseases

IN SITU LUNG ULTRASOUND TO RULE IN HEART FAILURE PATIENTS: DIAGNOSTIC ACCURACY AND CORRELATION WITH EMERGENT CARDIAC BIOMARKERS

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1. Summary

Heart failure (HF) affects 2% of the adult population in developed countries and its prevalence increases exponentially with age. In Catalonia, it is estimated that there are 88,000 people with HF. Taking into account that people > 65 years will double in the next 20 years, this pathology should be managed from all levels of care.

HF is the leading cause of hospitalization of people over 65 years. A frequent cause of hospitalization is the delay in recognition of congestion signs. In clinical practice, we have different elements (clinical, imaging and laboratory) that allow us to make a diagnostic approach but all of them have limitations.

In this context, it is necessary to develop new non-invasive diagnostic tools available at the patient's bedside to improve our current diagnostic limitations in HF. In situ lung ultrasound (LUS) and new cardiac biomarkers that have appeared in recent years could add precision to the current diagnostic algorithm.

This project aims to show the usefulness and diagnostic accuracy of LUS performed in situ in two clinical scenarios: to rule in HF both as a de novo diagnosis in outpatients as well as in decompensation from chronic HF, together with two emerging biomarkers in addition to LUS and conventional assessment. We hypothesize that LUS is a valid alternative for the assessment of pulmonary congestion of ambulatory patients with HF. During the development of the project, the study was extended with a third scenario to assess the prognostic impact of LUS in patients with stable chronic HF. LUS has been performed at the bedside with a pocket device (V-scan with a single sector probe, General Electric®). In scenario 1 (clinical suspicion of HF in primary care), two LUS protocols were evaluated: LUS-C1, with 8 thoracic areas explored; LUS-C2, with 12 thoracic areas explored by adding 4 infero-posterior areas. For the analysis, an LUS was considered positive if bilaterally there were 2 positive areas of 4 in the LUS-C1 protocol and 2 positive areas of 6 in the LUS-C2 protocol (positive thoracic area if ≥ 3 B lines). In scenario 2 (suspected HF decompensation) and in patients with stable chronic HF, the protocol recommended by the international consensus (LUS-C1, 8 thoracic areas) was used. For the analysis, the number of lines in each thoracic area was counted and the sum of lines was evaluated.

Our results show that LUS is useful for "rule-in" of HF in outpatients with suspected de novo HF in primary care, adds value to the standard diagnostic algorithm, especially when natriuretic peptides are not available, and requalifies a third of patients compared to the Framingham criteria and ECG, in the absence of NT-proBNP (scenario 1).

In addition, PD is useful for diagnosing patients with suspected decompensation of HF and allows monitoring the evolution of decompensation. On the other hand, the number of B lines is correlated with biomarkers such as NT-proBNP, CA125 and ST2 (scenario 2). Finally, the number of B lines is independently associated with death from any cause in patients with stable chronic HF.

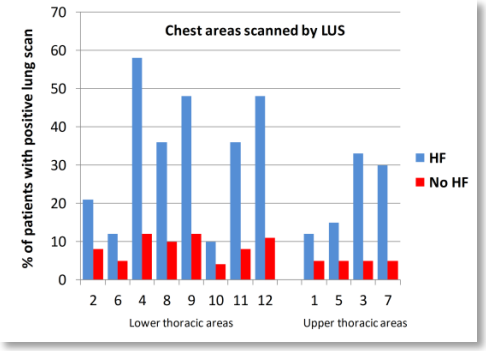
In conclusion, this project shows that in situ LUS adds value and improves the diagnostic accuracy of HF process, both in the diagnosis of non-acute de novo HF and also in chronic HF decompensation. In patients with stable chronic HF it is an independent prognostic marker and helps prognostic stratification with other clinical variables in the absence of NT-proBNP.

2. Results

Scenario 1: CLINICAL SUSPICION OF HEART FAILURE IN PRIMARY CARE

223 patients evaluated: 4 excluded by pulmonary fibrosis (post-hoc diagnosis), 54 due to an increase in the dose of diuretic prior to LUS and 3 due to not having performed the echocardiogram (162 patients included)

Two LUS criteria (C) of congestion were investigated: LUS-C1, 2 of 4 anterolateral positive areas in each hemithorax (recommended criterion); LUS-C2: 2 of 6 anterolateral and posterior positive areas each hemithorax.



Patients with HF had higher percentages of positive exams in the lower zones of the hemithorax, especially in the lateral and posterior areas.

	Se	Sp	PPV	NPV	LR +	LR -	Accuracy
LUS-C1	0.12	0.99	0.80	0.82	12	0.88	0.81
LUS-C2	0.33	0.99	0.92	0.85	33	0.67	0.86

LUS PPV (0.92) showed that it is useful in the rule-in HF diagnosis in primary care.

Area under the curve of different complementary examinations combinations, and LUS reclassification

	Accuracy	95% CI
Symptoms/signs +ECG	0.75	0.65–0.84
Symptoms/signs+ECG+NP	0.84	0.77–0.90
Symptoms/signs+ECG+LUS-C2	0.85	0.77–0.92
Symptoms/signs+ECG+NP+LUS-C2	0.90	0.84–0.93

LUS-C2 added to Framingham criteria + ECG allowed reclassifying 33% of patients [NRI 0.65 (95% CI 0.04-1.1), IDI 0.19 (95% CI 0.04-0.37)]. LUS-C2 added to Framingham criteria + ECG + NT-proBNP reclassified 29% of patients [NRI 12:58 (95% CI -0.38-1.03), IDI 12:17 (95% CI 0.02-0.31)].

LUS and bio-markers

	NT-proBNP	GDF15	hsTnT	CA125	hsPCR	IL6	IL33	IL1B	sNEP	sST2	TNFα	TNFRSF 1A
Rho	0.3	0.3	0.2	0.1	0.2	0.3	-0.03	-0.1	-0.1	0.2	0.7	0.2
p	<0.001	<0.001	0.004	0.2	0.1	<0.001	0.7	0.1	0.9	0.5	0.4	0.1

NT-proBNP, N-terminal pro-B-type natriuretic peptide; GDF15, growth differentiation factor 15; hsTnT, high-sensitivity troponin T; CA125, cancer antigen 125; IL, interleukin; NEP, soluble neprilysin; sST2, soluble suppression of tumorigenicity 2; TNFα, tumor necrosis factor α; TNFRSF1A, TNF receptor Superfamily Member 1A

Scenario 2: ASSESSMENT OF HEART FAILURE DECOMPENSATION

239 suspected decompensations in 194 patients: 160 patients with 1 suspicion, 26 patients with 2 suspicions, 5 patients with 3 suspicions, and 3 patients with 4 suspected decompensations.

LUS was repeated in 100 decompensations considered clinically compensated by the cardiologist in charge (clinical recompensation) and in 80 decompensations at one month of the clinical recompensation.

Of the 239 suspected decompensation, the cardiologist in charge of the evaluation considered that 59 were not HF decompensations, 50 were left HF decompensation, 70 right HF decompensation and 60 biventricular HF decompensation.

Median B-lines of the cohort were 14.5±11.8.

LUS (n=239)	
Chest zone 1	1.4±2
Chest zone 2	1.7±2
Chest zone 3	1.5±2.2
Chest zone 4	3±1.6
Chest zone 5	1.2±1.6
Chest zone 6	1.8±2
Chest zone 7	1.8±2
Chest zone 8	3.1±3.1
All	14.5±11.8

Number of B-lines	
Not HF decompensation	4.25 ± 6.2
Left HF	19.94 ± 11.46
Right HF	13.74 ± 9.96
Biventricular HF	21.0 ± 11.33
All	14.52 ± 11.83

P<0.001

Median B-line of the cohort considered clinically recompensated was 8.75 ± 8.
Median B-lines at one month of clinical recompensation was 9.81 ± 9.35
Statistically significant differences were found in paired data of decompensations and clinical recompensation: 17 ± 11 vs. 8 ± 8 (p <0.001)

Comparisons between B lines according to the type of decompensation

Not HF decompensation	**Left HF** **Right HF** **Biventricular HF**	<0.001 <0.001 <0.001
Left HF	**Right HF** **Biventricular HF**	0.011 0.96
Right HF	**Biventricular HF**	0.001

LUS and bio-markers

	NT-proBNP	**CA125**	**sST2**
Rho	0.51	0.51	0.43
p	<0.001	<0.001	<0.001

NT-proBNP, N-terminal pro-B-type natriuretic peptide; CA125, cancer antigen 125; sST2, soluble suppression of tumorigenicity 2.

STABLE CHRONIC HF PATIENTS

570 patients evaluated, mean follow-up of 31 ± 7.1 months

111 deaths (26 of which due to HF) and 74 patients suffered at least one admission due to HF.

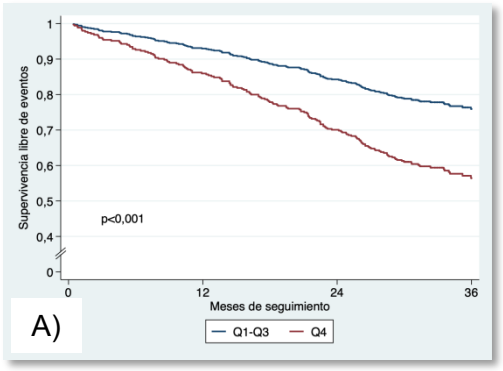
The primary outcome of death from all causes or hospitalization for HF occurred in 157 patients, while the compound of death or admission for HF in 83 patients.

Multivariable Cox regression including clinical covariables, without and with NTproBNP, for the primary composite final outcome and for all-cause death.

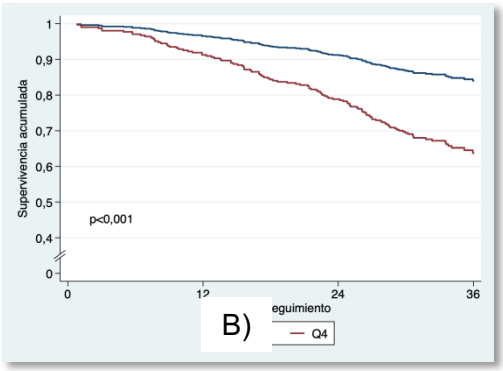
	Resultado final primario*			Muerte por todas las causas		
	HR	IC-95%	p	HR	IC-95%	p
Suma de líneas B	1,04	1,02 – 1,06	0,002	1,04	1,02 –1,07	0,001
Edad, años	1,03	1,02–1,05	<0,001	1,05	1,03–1,08	<0,001
Sexo femenino,	--	---	--	--	---	--
Etiología isquémica	1,64	1,19–2,25	0,002	1,75	1,17–2,62	0,007
Duración IC[a]	1,29	1,06–1,57	0,01	--	---	--
Clase NYHA	1,82	1,33–2,48	<0,001	1,59	1,09–2,32	0,02
FEVI, %	--	---	--	0,98	0,97–1,00	0,04
Diabetes	--	---	--	--	---	--
Hipertensión	--	---	--	--	---	--
Fib/Flut auricular	--	---	--	--	---	--
Anemia[b]	--	---	--	1,85	1,26–2,73	0,002
Insuficiencia renal[c]	1,68	1,15–2,46	0,008	--	---	--
IMC, Kg/m^2	--	---	--	--	---	--
IECA o ARA2	0,50	0,34–0,72	<0,001	--	---	--
Beta-bloqueantes	--	---	--	0,45	0,26–0,80	0,007
Hidralazina	--	---	--	2,48	1,63–3,77	<0,001
Nitratos	--	---	--	--	---	--

	Resultado final primario*			Muerte por todas las causas		
	HR	IC-95%	p	HR	IC-95%	p
Suma de líneas B	1,03	1,01 – 1,05	0,01	1,04	1,01 –1,06	0,008
Edad, años	1,03	1,01–1,05	0,001	1,04	1,02–1,06	<0,001
Sexo femenino,	--	---	--	--	---	--
Etiología isquémica	1,59	1,16–2,20	0,004	1,81	1,22–2,68	0,003
Duración IC	1,28	1,06–1,55	0,01	--	---	--
Clase NYHA	1,59	1,16–2,18	0,004	1,54	1,05–2,26	0,03
FEVI, %	--	---	--	--	---	--
Diabetes	--	---	--	--	---	--
Hipertensión	--	---	--	--	---	--
Fib/Flut auricular	--	---	--	--	---	--
Anemia	--	---	--	1,66	1,12–2,46	0,01
Insuficiencia renal‡	--	---	--	--	---	--
IMC, Kg/m^2	--	---	--	--	---	--
IECA o ARA2	0,54	0,37–0,78	0,001	--	---	--
Beta-bloqueantes	--	---	--	0,48	0,27–0,83	0,009
Hidralazina	--	---	--	11,66	1,21–1,95	0,03
Nitratos	--	---	--	--	---	--
NTproBNP	1,59	1,32-1,91	<0,001	1,54	1,21–1,95	<0,001

Event-free survival curves for the composite clinical outcome (death from any cause or hospitalization for HF) (A), and for death from any cause (B). Patients have been divided into quartiles (Q) of the sum of lines B, and Q4 has been compared against Q1-3.



Q4 (≥8 B-lines) doubled the risk of suffering the primary compound event (HR 2.08 [CI95% 1.50-2.88]; p <0.001)



Q4 (≥8 B-lines) doubled the risk of all-cause death (HR 2.59 [CI95% 1.77-3.78]; p<0.001).

3. Relevance and clinical implications of the results

SCENARIO 1: CLINICAL SUSPICION OF HEART FAILURE IN PRIMARY CARE

This is the first lung ultrasound work performed in outpatients without prior diagnosis of HF in primary care

Clinical implications: Our results support the usefulness of lung ultrasound in the diagnosis of HF as a complementary test added to the conventional methods used in primary care. Lung ultrasound in this scenario improves diagnostic resolution because:

- It is useful for "rule-in" IC in outpatients with suspected non-acute de novo HF.
- It adds value to the standard diagnostic algorithm of HF in primary care, especially when natriuretic peptides are not available.
- It requalifies one third of the patients compared to the Framingham criteria and abnormal ECG, in the absence of NT-proBNP.
- If integrated into the diagnostic algorithm of patients with clinical suspicion of HF, it could avoid delays in performing echocardiograms.

SCENARIO 2: ASSESSMENT OF HEART FAILURE DECOMPENSATION

Clinical implications: Our results show that lung ultrasound is useful in the differential diagnosis of patients with suspected decompensation of HF and allows monitoring the evolution of decompensation.

In addition, the number of B lines is correlated with biomarkers consolidated in IC with prognostic value and whose increase is known in decompensation situations such as NT-proBNP (<0.001), CA125 (<0.001) and ST2 (<0.001).

STABLE CHRONIC HF PATIENTS

Clinical implications: Our results show that B-lines are related to the composited end point of all-cause death or hospitalization due to HF and mortality due to any cause, and the statistical significance remains in a multivariable analysis that includes clinical and biomarkers (NT-proBNP).

In usual clinical practice we do not have access to an NT-proBNP point-of-care and, in addition, the determination of natriuretic peptides is not universally extended in all healthcare settings. In situ lung ultrasound helps to the prognostic stratification together with other clinical variables in the absence of NT-proBNP, and it is a simple, cheap and available exploration.

4. Scientific bibliography

Publications

Conangla L, Domingo M, Lupón J, Wilke A, Juncà G, Tejedor X, Volpicelli G, Evangelista L, Pera G, Toran P, Mas A, Cediel G, Verdú JM, Bayes-Genis A.
Lung ultrasound for heart failure diagnosis in primary care.
Journal of Cardiac Failure (1st revision)

Domingo M, Conangla L, Lupón J, de Antonio M, Moliner P, Santiago-Vacas E, Codina P, Zamora E, Gonzalez M, Diaz V, Rivas C, Velayos P, Santesmases J, Pulido A, Crespo E, Bayes-Genis A.
Lung ultrasound prognosis in chronic stable ambulatory heart failure patients
In preparation for the Revista Española de Cardiologia

Domingo M, Conangla L, Lupón J, de Antonio M, Moliner P, Santiago-Vacas E, Codina P, Zamora E, Gonzalez M, Diaz V, Rivas C, Velayos P, Santesmases J, Pulido A, Crespo E, Bayes-Genis A.
Lung ultrasound in heart failure decompensation assessment
In preparation for the European Journal of Heart Failure

Congresses (28 national congresses and 19 international ones)

SCENARIO 1: CLINICAL SUSPICION OF HEART FAILURE IN PRIMARY CARE
HF congress of European Society of Cardiology (Vienna, 2018): poster
30è Congrés de la Societat Catalana de Cardiologia (Barcelona, 2018): oral presentation.
World Conference of Family Doctors (WONCA) (Seoul, 2018): oral presentation.
Congreso de las Enfermedades Cardiovasculares de la Sociedad Española de Cardiología (Seville, 2018): poster (hub poster)

SCENARIO 2: ASSESSMENT OF HEART FAILURE DECOMPENSATION
HF congress of European Society of Cardiology (Athens, 2019): poster
30è Congrés de la Societat Catalana de Cardiologia (Barcelona, 2019): poster
Congress of the European Society of Cardiology (Paris, 2019): mini oral presentation
Congreso de las Enfermedades Cardiovasculares de la Sociedad Española de Cardiología (Barcelona, 2019): oral presentation

Doctoral thesis

"Validez de la ecografía torácica en el diagnóstico de la Insuficiencia Cardiaca en Atención Primaria".

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