A Five-Step Vascular Ultrasound Examination in Heart Failure: The First Two Years of the "ABCDE" G-SIUMB Multicenter Study 2018-2022

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Abstract: The aim of this study is the creation of a 5-step ultrasound examination to evaluate and monitor Heart Failure (HF) patients during hospitalization and follow-up. "ABCDE" is the acronym of an Italian multicentre study composed of a consecutive sample of HF patients admitted from the Emergency to the Internal Medicine/Geriatric Departments of several Italian hospitals. The "ABCDE" score includes the evaluations of A, the Ankle-brachial index (ABI), B, the B-lines, C, the Carotid intima media thickness (CIMT), D, the Diameter of the abdominal aorta and of the inferior cave vein and E, the echocardiographic assessment of the ejection fraction. This paper reports the preliminary results. Up to now, the "ABCDE" multicenter study seems an exciting opportunity to create an integrative ultrasound approach in HF. The definitive confirmation of these preliminary results and the effective usefulness of the "ABCDE" will be available in 2022, at the end of the study. (Curr Probl Cardiol 2021;46:100578.)

Introduction

Heart failure (HF) is a clinical syndrome characterized by typical symptoms and signs caused by structural and/or functional abnormalities, resulting in a reduced cardiac output and/or

elevated intracardiac pressures at rest or during stress.[1] The prevalence of HF is approximately 1%-2% of the adult population in developed countries, rising to ≥10% among people >70 years of age and it is the leading cause of hospitalization.[2]

We have previously explored[3] why an integrative ultrasound approach in HF should be mandatory both for hospitalized patients and in the follow up. In fact, an integrative ultrasound approach may be used as a recovery monitoring instrument at the bedside and also as a global cardiovascular assessment tool for these patients.

The Authors plan a 5-step ultrasound examination to evaluate and monitor HF patients during hospitalization and follow-up. They call this examination: the "ABCDE." It includes the evaluations of A, the Ankle-brachial index (ABI), B, the B-lines, C, the Carotid intima media thickness (CIMT), D, the Diameter of the abdominal aorta and of the inferior cave vein and E, the echocardiographic assessment of the ejection fraction. The "ABCDE" represents an integrative ultrasound approach in Internal Medicine/Geriatric departments.

The endpoints of the "ABCDE" examination are primarily related to the bedside evaluation in monitoring HF recovery (the association between each item of the "ABCDE" and the discharge time; the association between B,D, for cave vein, and E assessment and the number of diuretics shifts during hospitalization and recovery from HF; the association between B,D, for cave vein, and E assessment and natriuretic peptide variations and calculated ratio of arterial oxygen partial pressure to fractional inspired oxygen,PaO2/FiO2 ratio, at admission and discharge).

Secondary endpoints are related to the global cardiovascular assessment of the HF patient (the association between each item of the "ABCDE" and the number of "events" as death from any cause or readmission for HF in the follow-up period; the role of A, C and D, for the aorta, in the classification of the global cardiovascular risk for the HF patient).

This article reports the preliminary results of the first 2 years of the Italian multicentre study "ABCDE," that is planned to be concluded in 2022. This study is promoted by the Società Italiana di Ultrasonologia in Medicina e Biologia (SIUMB).

Methods

Ethical approval: All procedures are in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable

ethical standards. The Ethical Committee of Verona and Rovigo (Protocol Number 1703CESC) approved the study. The study has been posted to Clinicaltrials.gov (number: NCT03771209). Informed consent was obtained from all individuals participants included in the study.

Study Type, Setting, Population and Description of the Protocol

The "ABCDE" is a clinical trial with an estimated enrolment of 480 participants.

The study started in 2018 and the estimated study completion date is end 2022.

Ages eligible for the study are 18-90 years old.

The study population is composed by patients admitted from the Emergency Department to the Internal Medicine/Geriatric Departments with the clinical diagnosis of HF. The promoter center (Principal Investigator site) is the Internal Medicine of the University of Verona (Italy).

At the moment, the recruitment is active in 5 Italian centere (Internal Medicine of the University of Verona, Internal Medicine of the University of Perugia, Internal Medicine of the University of Palerrmo, Geriatric Unit of the University of Verona and Internal Medicine of the Negrar Hospital, Verona).

Exclusion criteria are concomitant acute coronary syndrome, pneumonia, chronic obstructive pulmonary disease, lung cancer or metastases, lung fibrosis, previous pneumonectomy or lobectomy, breast prothesis, obesity. These exclusion criteria are selected as potential confounders in NT-proBNP levels and in order to avoid the detection of B-lines other than due to HF.

Figure 1 represents the flow chart of the "ABCDE" study.

Venous blood samples are collected from each subject for routine examination on admission − hemoglobin and white blood cells count, serum creatinine, sodium, potassium, urea, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, glucose, C-reactive protein (measured with standard methods).

Moreover, NT-proBNP dosage is obtained on admission and on discharge.

Urine output and diuretic dosage will be carefully reported daily. Arterial blood samples are collected on admission and on discharge to test the PaO2/FiO2 ratio (the calculated ratio of arterial oxygen partial pressure to fractional inspired oxygen) as indicator of HF severity (on admission) and recovery (on discharge).
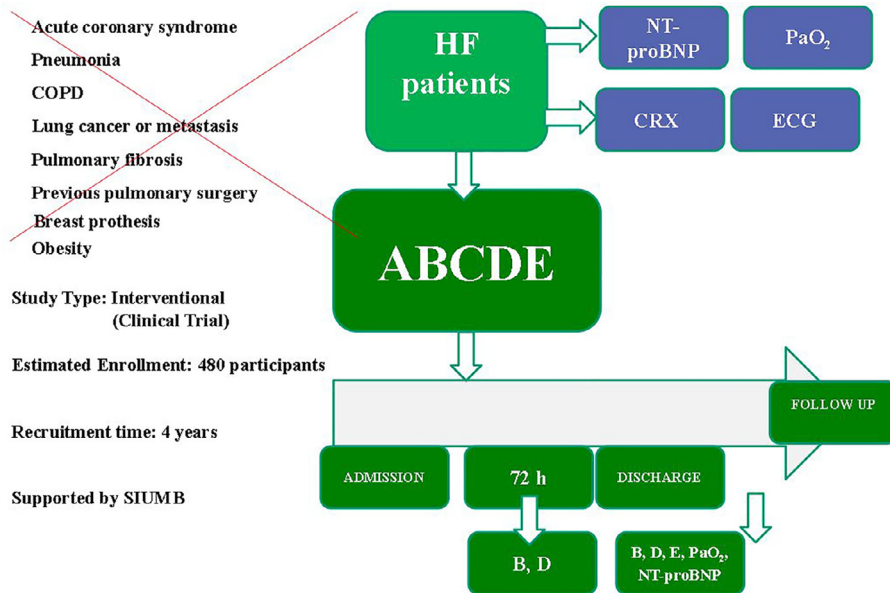
FIG 1. The "ABCDE" study flow chart. COPD, chronic obstructive pulmonary disease; CRX, chest radiography; HF, heart failure; NT-proBNP, the amino-terminal portion of B type natriuretic peptide; PaO$_2$, partial pressure of oxygen in arterial blood; SIUMB, Società Italiana di Ultrasonologia in Medicina e Biologia.

An electrocardiogram recording and chest radiography examination are obtained on admission.

Ultrasound Examinations

The "ABCDE" examination includes the evaluations of A, the Ankle-brachial index (ABI), B, the B-lines, C, the Carotid intima media thickness (CIMT), D, the Diameter of the abdominal aorta and of the inferior cave vein (ICV) and E, the echocardiographic assessment of the ejection fraction. Patients undergo: A (calculated for each leg at admission), B-lines counting (calculated at admission, during hospital stay and at discharge, approach 72 spaces), C (at admission), D (at admission for the aorta and at admission, during hospital stay and at discharge for the ICV) and E (at admission and discharge).

The "ABCDE" evaluation is performed by Internal Medicine/Geriatric specialists already certified by SIUMB. The operators work in contact, planning dedicated meetings in order to reduce the interobserver variability in the different centers.

Table 1 represents the "ABCDE" score, as suggested by the Authors on the basis of the current literature data,[3] as a 5-step vascular ultrasound examination in HF patients. A score is awarded according to the severity of each item.

The following are the detailed procedures of ultrasound evaluations.

A. The method of measuring and the interpretation of the results (normal, mild-moderate severe obstruction) of the ankle-brachial index is made according to previous works.[4,5]
B. Lung ultrasound examinations for the B-lines detection are performed with patients in the supine or near-supine position for the anterior scanning, and in the sitting position for the dorsal scanning. A B-lines score, defined as the total number of the detectable B-lines, is determined, according to the approach proposed by Gargani and Volpicelli[6,7] and already confirmed in a previous work by our group.[8]
C. CIMT is evaluated as the distance between the leading edge of the lumen-intima interface and the leading edge of the media adventitia interface, according to the recommendations of the Mannheim Carotid Intima-Media thickness Consensus.[9] The investigators perform not invasive measurements of CIMT using a high-resolution B-mode ultrasound equipped with a 7.5- to 12-MHz probe. For all subjects, CIMT is measured in the far wall of the common carotid artery

TABLE 1. The "ABCDE" score

A (ANKLE-BRACHIAL INDEX)
Normal (<90): points 0
Mild obstruction (0.71-0.90): points 1
Moderate obstruction (0.41-0.70): points 2
Severe obstruction 0-0.40: points 3
B (B-LINES)
Number of B-lines for each space ≤5: points 0
Number of B-lines for each space ≥ 6 to ≤9: points 1
Number of B-lines for each space ≥10 ("Full white screen"): points 3
C (IMT OR CAROTID PLAQUE)
Normal: points 0
Altered IMT (>0.9 mm): points 1
Plaque presence (no significant stenosis, <70% following NASCET classification): points 2
Plaque presence (significant stenosis, >70% following NASCET classification): points 3
D (DIAMETER OF AORTA AND CAVE VEIN COLLAPSIBILITY INDEX)
Aorta
Normal (<25 mm): points 0
Normal diameter but with calcifications: points 1
Ectasia (25-30 mm): points 2
Aneurysm (>30 mm): points 3
Cave vein
Normal collapsibility index (40%-75%): points 0
Altered collapsibility index (if <40% or >75%): points 1
E (EJECTION FRACTION ACCORDING TO ESC GUIDELINES 2016)
HFpEF (LVEF ≥50%): points 0
HFmrEF (LVEF in the range of 40%-49%): points 1
HFrEF (LVEF <40%): points 2

ESC, European Society of Cardiology; HFpEF, heart failure with preserved ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; HFrEF: heart failure with reduced ejection fraction; IMT, Carotid intima media thickness; NASCET, North American Symptomatic Carotid Endarterectomy Trial; LVEF, left ventricular ejection fraction.

proximal to the bifurcation, at the bulb and the origin of the internal carotid artery of both sides. On each arterial site, mean CIMT values (as averaged across the entire distance) and maximal CIMT values are recorded and assessed by automatic software for CIMT measurement. The presence of the plaque is evaluated and described as previously stated.[10]

D. ICV maximum and minimum diameter and its collapsibility index (Inferior Cave Vein Collapsibility Index [ICVCI]) are measured in subcostal view in M-mode, 2 cm from the right atrial junction. ICVCI is calculated according to the formula [(ICV max-ICV min)/ ICV max] x 100. The ICVCI% cut-offs are: >75 (hypovolemia), ≥40 and ≤ 75 (euvolemia) and <40 (hypervolemia).[11] Abdominal aorta evaluation is conducted as previously described.[12-14]

E. Transthoracic echocardiography is performed in order to classify patients with normal left ventricular ejection fraction (LVEF) (≥50%, HF with preserved EF [HFpEF]), patients with reduced LVEF (<40%, HF with reduced EF [HFrEF]), patients with an LVEF in the range of 40%-49% (HFmrEF)[1]. Simpson biplane method[1,15] is used.

Data are collected from each center. The modality "*Google moduli,*" an on-line sharing data platform, is used to send the data to the Principal Investigator's center in Verona.

Statistical Analysis

The patients' characteristics at admission and at discharge are summarized as percentages or means (SD), accordingly to their distribution. Differences in diastolic and systolic blood pressure and the PaO2/FiO2 ratio between admission and discharge are tested with paired Student *t*-tests (alpha = 0.05). Multiple Poisson regression models, adjusted for age and sex, are fitted to evaluate the associations of the number of days of hospitalization (from admission to discharge) and the number of diuretic dosage modulations with the following patients' characteristics at admission: (1) log(B-lines); (2) ICVCI (0 = euvolemia; 1 = hypo/hypervolemia); (3) ejection fraction; (4) ABI; (5) CIMT groups; (6) aorta diameter (0 = normal; 1 = impaired). Center is considered as clustering factor and cluster-robust standard errors were used. The correlations of PaO2/FiO2 ratio with log(B-lines) and log (NT-proBNP) are assessed using linear regression models including both data on admission and discharge with cluster-robust standard errors to take into account the intrapatient variability. Statistical analyses are performed using STATA 14.2 (Stata Corp. College Station, TX).

Results

The demographic and clinical characteristics of the 63 enrolled patients on admission and discharge are reported in Table 2.

The PaO2/FiO2 ratio increases at discharge, as indicator of clinical recovering from HF. The average recovery time is 8.94 days.

Figure 2 shows the associations between PaO2 and the B-lines on admission and discharge and PaO2 and NT-proBNP on admission and discharge (both expressed in log10).

The B-lines are strongly associated with the levels of PaO2, as log10 (B-lines) predicted 22% of the variability of PaO2/FiO2 ratio ($R2 = 0.2221$; $P < 0.001$). On the other hand, the association between

TABLE 2. Enrolled patients' features at admission/discharge

n = 63	Admission	Discharge	P value
Age (years)	82,5 (7,53)		
Gender (females)	31 (49.21%)		
Smoke			
• Former	37 (58,73%)		
• Current	4 (6,35%)		
• Never	22 (34,92%)		
Comorbidities			
• Ischemic heart disease	22 (34,92%)		
• Hypertension	53 (84,13%)		
• Valvular heart disease	23 (36,51%)		
• Diabetes Mellitus	27 (42,86%)		
• Peripheral vascular disease	18 (28,57%)		
• Dyslipidemia	24 (38,10%)		
• Ace-Inhibitors	27 (42,86%)		
• β-blockers	42 (66,67%)		
• Diuretics	45 (71,43%)		
• Calcium-channel blockers	4 (6,35%)		
• Anti-coagulants	37 (58,73%)		
• Anti-aggregants	19 (30,16%)		
• Statins	32 (50,79%)		
• Nitrates	11 (17,46%)		
SBP (mm Hg)	137,24 (21,86)	122,70 (14,42)	<0.01
DBP (mm Hg)	75,62 (11,96)	70,57 (11,49)	0.013
Heart rate (bpm)	85,97 (22,38)	75,72 (13,95)	<0.01
Serum Creatinine (mg/dL)	1,24 (0,65)	1,20(0,75)	0.064
PaO_2/FiO_2 ratio	261,60 (66,05)	341,56 (70,63)	<0.01
ECG			
• Atrial Fibrillation	32 (50,79%)		
• Sinus Rhythm	24 (38,10%)		
• Other Rhythm	7 (11,11%)		
Chest X-Ray			
• Vascular Congestion	46 (73,02%)		
• Pleural Effusion	36 (57,14%)		
Type of HF			
• HFpEF	31 (49,20%)		
• HFmrEF	16 (25,40%)		
• HFrEF	16 (25,40%)		
HF days		8,94 (4,46)	

DBP, diastolic blood pressure; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFmfEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; PaO2/FiO2 ratio, the calculated ratio of arterial oxygen partial pressure to fractional inspired oxygen; SBP: systolic blood pressure. Data are expressed in n (%) or mean standard deviation (SD).

NT-proBNP and PaO2/FiO2 ratio is weaker, with log10 (B-lines) predicting only 1% of the PaO2 variability (R2 = 0.0187; P = 0.254).

Figure 3 depicts the associations among the duration of hospitalization, expressed in days, and 3 items of the "ABCDE" score.

An altered A is associated to a longer hospital stay, as happens for patients with carotid atherosclerosis. So, it may be argued that a worse vascular pattern influences the duration of HF recovery. On the other hand, the number of B-lines (at admission) is not associated to a longer hospital stay.

Figure 4 depicts the associations among the duration of hospitalization, expressed in days, and the other 3 items of the "ABCDE" score.

Alterations in abdominal aorta diameter is associated to a longer hospital stay. Alteration in cave vein diameter (that is ICVCI) is associated to a longer hospital stay (21% more, with borderline statistical significance). An improved E is associated to a shorter hospital stay (in particular, a 10% increase in E means a 13% shortening in hospital stay).

Finally, Figure 5 depicts the associations among the frequency of diuretic therapy changes and B-lines and ejection fraction.

B-lines number is associated to an increased number of diuretic dosage modulations. Patients with E >40% need decreased number of diuretic dosage modulations.

Discussion

The "ABCDE" study appears to be a great opportunity to explore and understand the role of a complete cardiovascular-focused ultrasound assessment in HF.

At the moment, not all the endpoints can be targeted, because of the small sample. The precise role of each item of the score system will be clarified only when the enrolment will be completed. Nevertheless, the importance of sharing these preliminary data is related to the fact that other centers may be addressed as potential contributors as participants.

These preliminary results reinforce the concept of the importance of a global cardiovascular ultrasound evaluation in HF at the bedside (no data available at the moment for the follow up).

According to the current guidelines,[1] echocardiography is considered the most useful and widely available test in HF patients. It provides immediate information on chamber volumes, ventricular systolic and diastolic function, wall thickness, valve function, and pulmonary hypertension. This information is crucial in establishing the diagnosis and in determining appropriate treatment. Nevertheless, the concept of using sonography as a real-time bedside clinical tool (point of care) in the hands of the same physician who is treating the patient is obtaining a growing consensus.[16] Among them, the quantification of the B-lines, is surely the most innovative and also the simplest to learn. Also cave vein monitoring
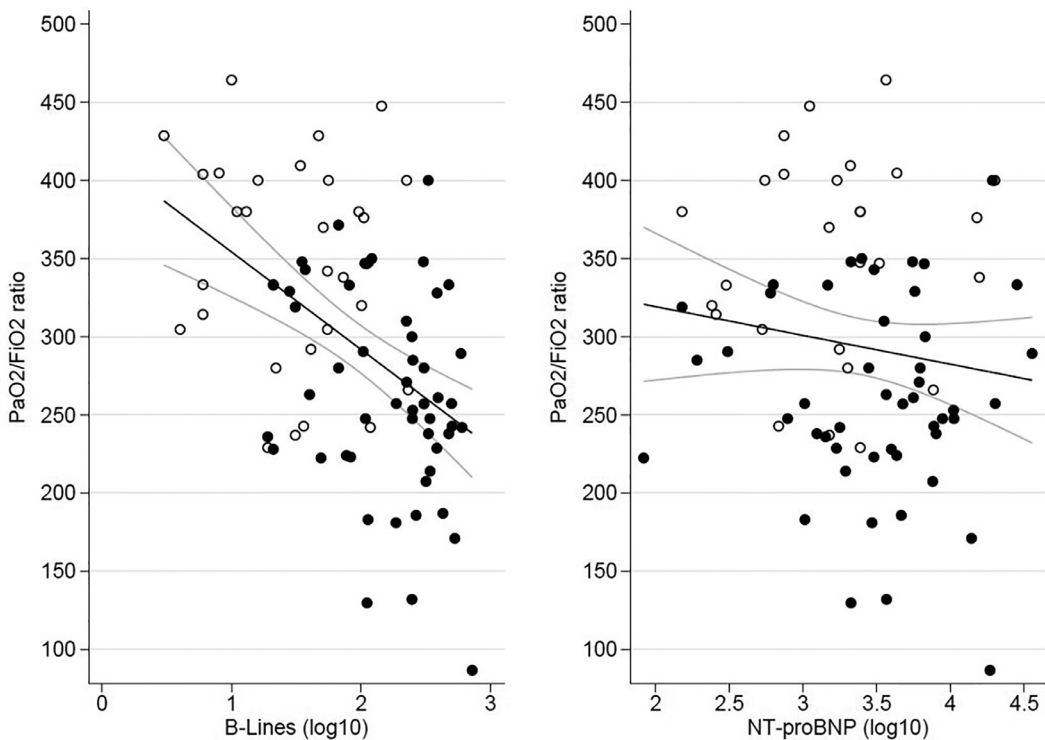
FIG 2. The associations between PaO_2/FiO_2 ratio and B-lines on admission and discharge (on the left), and PaO2/FiO2 ratio and NT-pro-BNP on admission and discharge (on the right). NT-proBNP: the amino-terminal portion of B type natriuretic peptide; PaO2/FiO2 ratio: the calculated ratio of arterial oxygen partial pressure to fractional inspired oxygen; black dots admission; white dots discharge. $R^2 = 0.2221$, $P < 0.001$ for the association between PaO2/FiO2 ratio and B-lines. $R^2 = 0.0187$, $P = 0.254$ for the association between PaO2/FiO2 ratio and NT-pro-BNP.
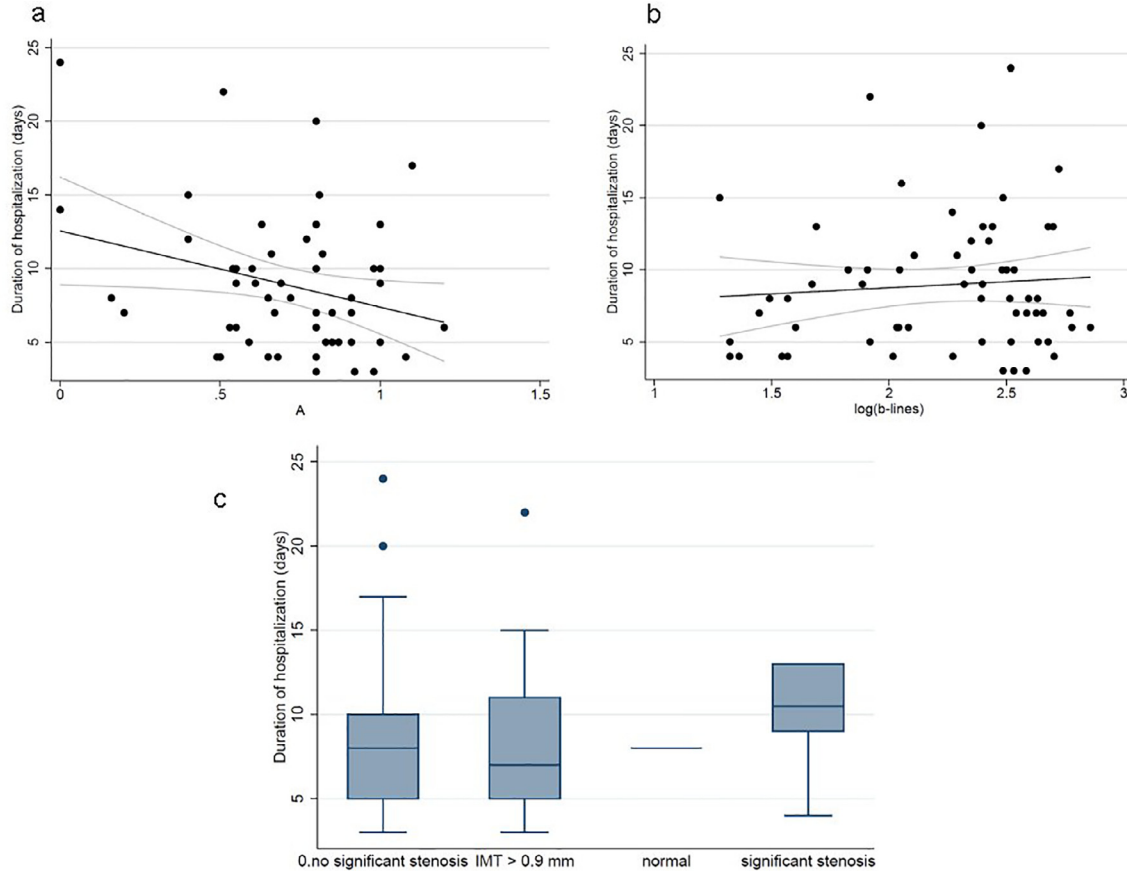
FIG 3. The associations among the duration of hospitalization (days) and A, ankle-brachial index (a), B-lines (b) and Carotid intima media thickness (c). A, Ankle-brachial index; IMT, carotid intima media thickness. $P < 0.001$ (a); $P = 0.471$ (b); $P = 0.021$ (c).
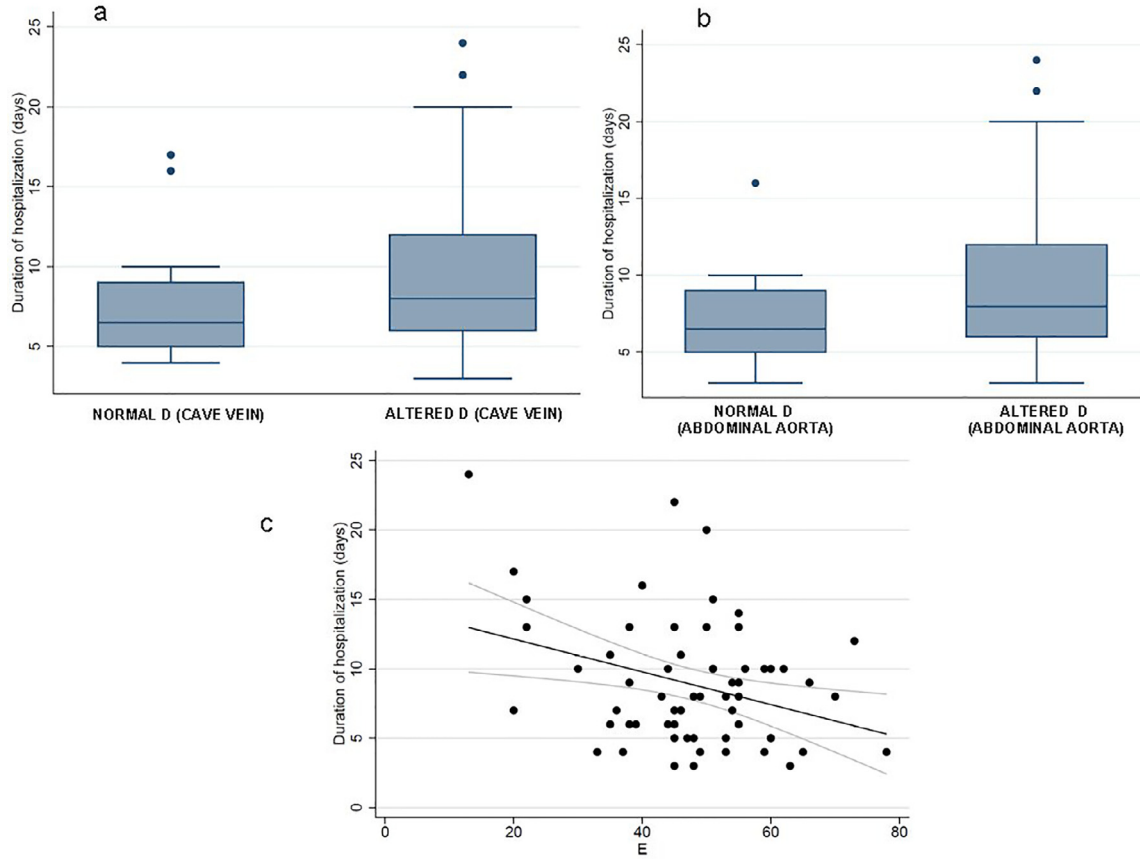
FIG 4. The association among the duration of hospitalization (days) and the diameter of cave vein (a), abdominal aorta (b), and ejection fraction (c). D, diameter; E, ejection fraction. $P = 0.056$ (a); $P < 0.001$ (b); $P < 0.007$ (c).
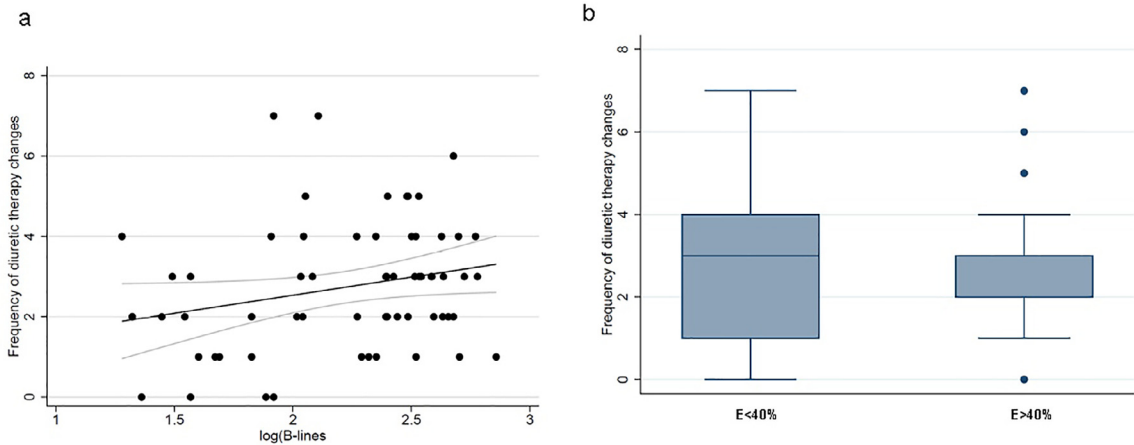
FIG 5. The associations among the frequency of diuretic therapy changes and B-lines (a) and ejection fraction (b). E, ejection fraction. $P < 0.001$ (a); $P = 0.011$ (b).

by the quantification of the ICVCI is considered an efficient tool in monitoring the congestion recovery in HF patients.[17]

We have previously demonstrated[8] the potential of lung ultrasound and of the quantification of ICVCI in tailoring diuretic therapy and speeding up the discharge time in HF hospitalization.

An important confirmatory result of this study concerns the B-lines and their role in monitoring HF recovery. The results of this study show a stronger association between PaO2/FiO2 ratio and B-lines compared to the association between PaO2/FiO2 ratio and NT-proBNP both on admission and on discharge. The B-lines are not clearly mentioned in HF ESC guidelines.[1] In these preliminary results of the "ABCDE" study, the reduction of the B-lines does not occur in accordance with the NT-proBNP levels, suggesting that serum NT-proBNP may not reliably indicate pulmonary congestion having been resolved. This result supports our previous[8] finding on this topic. NT-proBNP should be considered as useful marker for the discrimination of the possible origin of respiratory failure, but not a precise monitoring tool in HF recovery. NT-proBNP has proved to be effective only in excluding or confirming congestive HF. These data support the use of this molecule in the Emergency care setting rather than in the Internal Medicine/Geriatric department. Natriuretic peptides are affected by age,[18] body mass index,[19] myocardial ischemia and hypoxia even in the absence of left ventricular dysfunction,[20] hormonal dysfunctions,[21] renal failure, and diabetes.[22]

Nevertheless, the "ABCDE" study goes further. The cardiovascular risk assessment of these patients may include also the peripheral vessels examination. In this perspective, carotid, abdominal aorta, and peripheral arteries evaluation may represent the integrative approach on the basis of previous literature extensively reviewed in.[3]

At the moment the majority of these preliminary results are focused on the duration of the hospitalization. It is well known that the costs associated with HF hospitalization are consistent in the Internal Medicine/Geriatric Department.[23] Moreover, these costs are compounded by a high rate of readmission. The worst cardiovascular status (that is altered A-C-D in the "ABCDE" score) implies a longer hospital stay. This finding confirms that peripheral atherosclerosis plays a key role in HF, affecting the recovery time. Future results will clarify the precise role of each vascular alteration.

The importance of the bedside evaluation in the "ABCDE" study is crucial − the operator is not blinded to the patients' clinical conditions (while the Radiologist/Cardiologist usually has only an information summary about them). Furthermore, the possibility of performing the "ABCDE" at the bedside at any moment allows for an easier management

of the therapy. The study patients undergo diuretic dosage modulations according to the clearance of the B-lines, not only according to the clinical status. At the moment, diuretic therapy shifts seem to be very sensitive to altered ventricular function.

Conclusion

Up to now, no precise and integrated ultrasound score systems in HF have been proposed neither in hospitalized patient nor in the follow-up. To date, the "ABCDE" study is the first that examines a global ultrasound cardiovascular approach in HF. The fact that SIUMB is the promoting society of the study strengths its importance as leading and linking actor in ultrasound development in Italy.

Author Contributions

CM and MS conceived the study. GP performed the statistical analysis. DG reviewed the manuscript and the study design. CM wrote the paper.

Collaborators of the "ABCDE" Study

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Ethical Approval

All procedures are in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The Ethical Committee of Verona and Rovigo (Protocol Number 1703CESC) approved the study. The study has been posted to Clinicaltrials.gov (number: NCT03771209).

Informed Consent

Informed consent was obtained from all individuals participants included in the study.

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