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Early echocardiography by treating physicians and outcome in the critically ill: An ancillary study from the prospective multicenter trial FROG-ICU

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ABSTRACT

Purpose: This study aimed to investigate the association between the use of early echocardiography performed by the treating physician certified in critical care ultrasound and mortality in ICU patients.

Materials and methods: FROG-ICU was a multi-center cohort designed to investigate the outcome of critically ill patients. Of the 1359 patients admitted to centers where echocardiography was available, 372 patients underwent echocardiography during the initial 3 days.

Results: Of the ICU patients admitted for cardiac disease, 47.4% underwent echocardiography, and those patients had the lowest left ventricular ejection fraction 40 [31–58] % and the lowest cardiac output 4.2 [3.2–5.7] L/min compared to patients admitted for other causes ($p < 0.001$ for both). One-year mortality was 36.8% and 39.9% in patients with and without echocardiography, respectively [HR 0.92 (95% CI 0.75–1.11)]. This result was confirmed after multivariable Cox regression analysis [HR 0.88 (95% CI 0.71–1.08)]. Subgroup analyses suggest that among patients admitted to ICU for cardiac disease, those managed with echocardiography had a lower risk of one-year mortality [HR 0.65 (95% CI 0.43–0.98)].

Conclusions: Early echocardiography by treating physicians was not associated with short- or long-term survival in ICU patients. In subgroups, early echocardiography improved survival in ICU patients admitted for cardiac disease.

Trial registration: clinicaltrials.gov Identifier: NCT01367093.

Keywords:
Echocardiography
ICU
Critically ill
Mortality

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1. Introduction

Echocardiography is a recognized screening, diagnostic, and hemodynamic monitoring tool, in addition to its role in cardiovascular diagnosis [1]. The use of echocardiography has been reported in several studies to be beneficial not only for the diagnosis and management of patients with primary cardiac diseases, but also for patients with a wide range of critical conditions with haemodynamic instability [2-5]. Indeed, there are several systematic reviews and meta-analyses that report an association of outcomes with echo parameters in ICU patients. In ICU patients, weaning failure from mechanical ventilation was reportedly associated with the parameter of echocardiography indicating left ventricular diastolic dysfunction [6]. In patients with sepsis, some reported that mortality was associated with parameters of diastolic dysfunction and values of strain assessed with speckle-tracking echocardiography, while others reported no association with left ventricular ejection fraction (LVEF) or systolic wave obtained with Tissue Doppler Imaging [7-11]. The guidelines published by the European Society of Cardiology (ESC), the European Society of Intensive Care Medicine (ESICM), and the American Heart Association (AHA) recommend an early echocardiographic assessment for hemodynamically unstable patients admitted in intensive care units (ICU) [12-14]. However, there are few data on ICU patients comparing non-invasive hemodynamic according to cause(s) of ICU admission and on the association between the use of echocardiography in the early phase of the ICU stay and clinical outcomes [15-17]. Randomized controlled trials aiming to determine the impact of early echocardiography on patient outcomes are challenging. Indeed, physicians trained in critical care ultrasound would hardly accept to randomize critically ill patients with unstable hemodynamics to undergo echocardiography versus no echocardiography. Taking into account the above-mentioned lack of data, we investigated the association between the use of early echocardiography performed by the treating physician and mortality in a large prospective, observational, multi-center cohort of ICU patients.

2. Methods

2.1. Study design

This is an ancillary analysis from the French and euRopean Outcome reGistry in Intensive Care Units (FROG-ICU) study. The original work was a prospective, observational, multi-center cohort study that enrolled 2087 patients and was designed to assess the long-term survival rates of patients admitted to ICU. The study was approved by the local ethics committees (Comité de Protection des Personnes, Ile de France IV, IRB n°00003835 and Commission d'éthique biomédicale de l'hôpital de Louvain, IRB n° B403201213352) and registered on <https://clinicaltrials.gov/ct2/show/NCT01367093>. The methodology and results of the original study have been published previously [18,19].

2.1.1. Participants and inclusion criteria in the present study

The FROG-ICU study involved 21 medical, surgical or mixed ICUs. All consecutive patients admitted to ICU were screened for eligibility. Inclusion criteria were mechanical ventilation and/or administration of at least one vasoactive agent (except dopamine) for more than 24 h. The exclusion criteria of the original study were age < 18 years at admission, severe head injury, suspected brain death, pregnancy or breastfeeding, organ transplantation in the past 12 months, and lack of social security coverage [18]. For the present study, some patients were also excluded due to death during the first 3 days of ICU stay. For patients included in FROG-ICU, several baseline and clinical parameters were recorded in a specifically-designed data collection notebook.

2.1.2. Echocardiography

In an effort to investigate the effectiveness of echocardiography during an early phase, the study population was divided into 2 groups: the

Echocardiography group included patients with transthoracic echocardiographic (TTE) examination performed within 3 days of ICU admission, and the Non-Echocardiography group included patients who did not undergo echocardiography in the initial 3 days. Echocardiography was performed by the bedside physician in charge of the patients. Furthermore, regarding the level of echocardiography, the large majority of physicians were certified in critical care ultrasound. The parameters recorded included LVEF, mitral inflow early (E) and late diastolic (A) velocities, the E/A ratio, the pulsed wave tissue Doppler early diastolic velocity (e') of the mitral annulus (lateral part), the E/ e' ratio, left atrial diameter, cardiac output (CO) calculated using left ventricular outflow tract velocity-time integral, right ventricular dimension, transtricuspid pressure gradient, tricuspid annular plane systolic excursion, and inferior vena cava (IVC) size, and distensibility index of IVC, which was calculated as the ratio of (maximum diameter of IVC - minimum diameter of IVC) / minimum diameter of IVC, and expressed as a percentage [20].

2.1.3. Study outcomes

For this study, the primary outcome was to assess the association between the use of echocardiography within 3 days of ICU admission and one-year all-cause mortality after 3 days of ICU admission. Secondary outcome was an association between early echocardiography and in ICU mortality. For primary analysis, we excluded centers where echocardiography was not available.

2.2. Statistical analysis

Continuous variables are presented as medians with interquartile range, whereas categorical variables are presented as numbers and percentages. Comparisons of characteristics according to groups were conducted by using Mann-Whitney or Kruskal-Wallis test for continuous variables and Fisher exact test or χ^2 test for categorical variables. Outcomes of patients who got early echocardiography were compared to patients who did not by means of logistic regression (for in ICU mortality) and Cox regression analysis (for one-year all-cause mortality), and the results were expressed as odds ratio (OR) and hazard ratios (HR) with 95% confidence interval (CI), respectively. The prognostic value of echocardiography and non-echocardiography was examined in multivariable models for ICU mortality and all-cause mortality at one-year. Details of the multivariable models are presented in the supplementary material online.

To account for missing data, multiple imputations were used with 10 imputed datasets. Rubin's algorithm was used for averaging parameter estimates across the imputed datasets. We explored the robustness of the findings of the main analysis described above by recalculating outcomes in three different sensitivity analyses: 1) multivariable-adjusted Cox regression analysis was repeated after adding adjustment by center (analysis on 1359 patients); 2) multivariable-adjusted Cox regression analysis was repeated without excluding patients in centers where echocardiography were not available in ICU (analysis on 2059 patients); 3) multivariable-adjusted Cox regression analysis was repeated, restricting the Echocardiography group to those patients where the echocardiography was performed within 24 h of ICU admission (analysis on 1375 patients). Subgroup analysis according to the etiologies was carried out. In the multivariable-adjusted Cox regression model, we examined potential modifying factors for the main outcome (one-year all-cause mortality) that we thought could theoretically impact the echocardiography effect: history of heart failure, history of severe valvular disease, history of coronary artery disease, age (≥ 64 or < 64 years), SAPS II (≥ 53 or < 53), troponin T (≥ 49.2 or < 49.2 pg/mL), and N-terminal pro-B type natriuretic peptide (1400 or < 1400 pg/mL). Dichotomization was based on the median value of each continuous variable. A two-sided p -value < 0.05 was regarded as statistically significant. Because this was an exploratory study, a pre-hoc sample size calculation was not made. Statistical analyses were performed using R,

Table 1
Characteristics of the study population at inclusion.

	Total n = 1359	Missing values (%)	Echocardiography n = 372	Non-Echocardiography n = 987	p value
Demographic data at inclusion					
Age (year)	64 [52–75]	0.0	63 [51–74]	64 [52–75]	0.56
Male gender, n (%)	864 (64)	0.0	246 (66)	618 (63)	0.26
Body mass index (kg/m ²)	26.2 [23.0–30.5]	35.2	26.0 [22.5–30.0]	26.3 [23.1–30.7]	0.15
Body weight (kg)	76.0 [65.0–89.0]	11.9	76.0 [65.0–86.0]	76.0 [65.0–89.0]	0.31
Medical history					
Charlson score	3 [2–5]	0.0	3 [1–5]	3 [2–5]	0.032
Severe valvular disease, n (%)	59 (4)	0.1	22 (6)	37 (4)	0.099
Peripheral vascular disease, n (%)	139 (10)	0.1	43 (12)	96 (10)	0.32
Prior stroke, n (%)	76 (6)	0.1	22 (6)	54 (5)	0.79
Hypertension, n (%)	580 (43)	0.1	148 (40)	432 (44)	0.22
Coronary artery disease, n (%)	144 (11)	0.1	35 (9)	109 (11)	0.43
Chronic heart failure, n (%)	99 (7)	0.1	27 (7)	72 (7)	1.00
Pulmonary hypertension, n (%)	28 (2)	0.1	8 (2)	20 (2)	0.83
Diabetes mellitus, n (%)	265 (20)	0.1	61 (16)	204 (21)	0.09
Chronic obstructive pulmonary disease, n (%)	181 (13)	0.1	44 (12)	137 (14)	0.37
Smoking	365 (27)	0.1	109 (29)	256 (26)	0.22
Chronic renal disease, n (%)	163 (12)	0.1	48 (13)	115 (12)	0.51
Chronic liver disease, n (%)	125 (9)	0.1	26 (7)	99 (10)	0.092
Recent active malignant tumors, n (%)	184 (14)	0.1	38 (10)	146 (15)	0.032
Loss of autonomy, n (%)	61 (4)	0.1	16 (4)	45 (5)	1.00
Etiology					
Cardiac disease, n (%)	266 (20)	0.0	126 (34)	140 (14)	<0.001
Sepsis, n (%)	357 (26)	0.0	83 (22)	274 (28)	
Acute neurological disorder, n (%)	177 (13)	0.0	43 (12)	134 (14)	
Acute respiratory failure, n (%)	301 (22)	0.0	76 (20)	225 (23)	
Other, n (%)	258 (19)	0.0	44 (12)	214 (22)	
Severity score at ICU admission					
SOFA score	8 [5–10]	19.3	8 [5–11]	8 [5–10]	0.40
SAPS II	53 [40–66]	0.0	57 [44–69]	51 [38–65]	<0.001
Clinical presentation at inclusion					
Temperature (°C)	37.3 [36.7–37.8]	2.2	37.2 [36.6–37.8]	37.3 [36.8–37.8]	0.035
Systolic blood pressure (mmHg)	121 [108–138]	2.6	122 [109–138]	121 [108–138]	0.94
Diastolic blood pressure (mmHg)	61 [53–70]	2.6	61 [53–70]	61 [53–70]	0.79
Heart rate (/min)	92 [79–106]	3.5	92 [78–108]	92 [79–106]	0.86
Respiratory rate (breaths per minute)	20 [16–25]	23.6	21 [16–25]	20 [16–25]	0.067
Atrial fibrillation, n (%)	131 (11)	8.5	37 (11)	94 (10)	0.76
Inotrope or vasopressor, n (%)	940 (69)	0.2	276 (75)	664 (67)	0.010
Mechanical ventilation, n (%)	1296 (95)	0.0	355 (95)	941 (95)	1.00
PaO ₂ (mmHg)	89 [74–116]	9.0	88 [75–115]	90 [74–116]	0.80
FiO ₂ (%)	40 [30–50]	9.2	40 [30–50]	40 [30–50]	0.45
PaO ₂ / FiO ₂ ratio	232 [138–329]	17.6	221 [134–320]	234 [141–334]	0.28
Diuresis of 24 h (mL/24 h)	1300 [750–2188]	13.9	1330 [750–2200]	1300 [745–2135]	0.79
Laboratory findings at inclusion					
Sodium (mmol/L)	140 [137–143]	1.5	140 [137–143]	140 [137–143]	0.12
Potassium (mmol/L)	3.9 [3.6–4.3]	2.5	3.9 [3.6–4.3]	3.9 [3.6–4.2]	0.28
Urea (mmol/L)	8.6 [5.3–14.5]	5.4	8.6 [5.0–13.9]	8.5 [5.4–14.9]	0.32
Creatinine (μmol/L)	86 [60–154]	0.0	89 [60–155]	85 [61–153]	0.47
eGFR (mL/min/1.73m ²)	74.7 [38.9–114.0]	0.0	71.8 [39.4–112.1]	75.4 [38.7–115.1]	0.69
Urinary Albumin (mg/L)	383 [297–476]	0.7	384 [307–480]	382 [292–475]	0.57
Uric acid (μmol/L)	199.9 [123.9–305.2]	6.3	205.9 [129.0–313.2]	196.2 [122.2–303.8]	0.21
Bicarbonate (mmol/L)	24 [21–27]	13.0	23 [21–26]	24 [21–27]	0.31
Lactate (mmol/L)	1.3 [0.9–1.9]	16.1	1.2 [0.8–1.7]	1.3 [0.9–1.9]	0.029
White blood cell (/mm ³)	11,400 [8200–16,530]	5.4	11,200 [8000–16,000]	11,600 [8200–16,800]	0.13
Hemoglobin (g/dL)	10.2 [9.1–11.6]	3.2	10.3 [9.2–11.6]	10.2 [9.1–11.7]	0.69
Platelets (/mm ³)	164,000 [98,000–236,000]	3.9	154,000 [94,000–216,000]	167,000 [99,000–252,000]	0.011
Bilirubin (mmol/L)	12 [8–27]	27.0	12 [8–21]	13 [8–29]	0.40
Glycemia (mmol/L)	7.4 [6.2–9.2]	7.8	7.3 [6.2–9.3]	7.4 [6.2–9.2]	0.95
Total protein (g/L)	55 [49–61]	8.4	55 [49–60]	55 [49–61]	0.69
Troponin T (pg/mL)	49.2 [19.2–150.9]	0.7	69.2 [23.8–256.3]	44.0 [17.6–125.7]	<0.001
NT-proBNP (pg/mL)	1400 [386–5116]	0.7	2014 [541–7035]	1289 [355–4491]	<0.001
Bioactive-adrenomedullin (pg/mL)	67.1 [34.7–131.1]	0.8	68.5 [35.2–118.0]	66.6 [34.6–137.9]	0.57
Procalcitonin (ng/mL)	1.3 [0.3–6.2]	0.7	1.2 [0.4–7.2]	1.3 [0.3–5.8]	0.57
Interleukin-6 (pg/mL)	94.0 [41.6–256.0]	0.7	92.6 [46.7–249.2]	95.2 [40.7–265.7]	0.93
Cystatin C (mg/L)	1.4 [0.9–2.1]	0.7	1.3 [0.9–2.1]	1.4 [0.9–2.1]	0.14
Galectin 3 (ng/mL)	21.9 [14.5–34.8]	0.7	20.5 [13.8–33.3]	22.3 [14.8–35.1]	0.11
Soluble-ST2 (ng/mL)	364.1 [193.4–799.9]	1.5	340.8 [187.2–760.0]	376.6 [195.8–830.5]	0.31

Data are presented as the median [interquartile range] or number (percentage). eGFR, estimated glomerular filtration rate; FiO₂, fraction of inspired oxygen; ICU, intensive care unit; NT-proBNP, N-terminal pro-B type natriuretic peptide; PaO₂, partial pressure of arterial oxygen; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment. Bold p values denote statistical significance (p < 0.05).

version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) packages: mice v3.11.0 [21] and rms v6.1-0 [22].

3. Results

3.1. Patient characteristics during ICU stay

Of the 2087 patients included in the FROG-ICU cohort, 28 patients who died during the first 3 days of ICU stay were excluded; therefore, 2059 patients provided the key data included in the present analysis. Of the 1359 patients admitted to centers where echocardiography was available in the present study, 372 (27%) patients underwent echocardiography during the initial 3 days. Patient characteristics are summarized in Table 1. Both groups differed in several aspects; notably, patients with echocardiography compared with patients without had higher SAPS II (57 [44–69] vs. 51 [38–65], $p < 0.001$), higher troponin T (69.2 [23.8–256.3] pg/mL vs. 44.0 [17.6–125.7] pg/mL, $p < 0.001$), and higher N-terminal pro-B type natriuretic peptide (2014 [541–7035] pg/mL vs. 1289 [355–4491] pg/mL, $p < 0.001$). The median LVEF in the Echocardiography group was 51 [35–66]%. Of the ICU patients admitted for cardiac disease, 47.4% underwent early echocardiography. Echocardiography detected a marked deterioration in cardiac contractile function –especially LVEF and CO– in cardiac disease (LVEF: 40 [31–58]%, CO: 4.2 [3.2–5.7] L/min) compared to the other etiologies, namely sepsis, acute neurologic disorders, acute respiratory failure and other causes ($p < 0.001$ for both) (Table 2).

3.2. Association between echocardiographic examination and mortality at one year

The primary outcome, one-year all-cause mortality, was 36.8% in the Echocardiography group and 39.9% in the Non-Echocardiography group [HR 0.92 (95% CI 0.75–1.11) $p = 0.38$] (Fig. 1).

After adjustment for covariates associated with ICU mortality and one-year all-cause mortality in the multivariable model (Table S1), the OR for ICU mortality and HR for one-year all-cause mortality between the Echocardiography group and the Non-Echocardiography group were 0.78 (95% CI: 0.55–1.11; $p = 0.16$) and 0.88 (95% CI: 0.71–1.08; $p = 0.23$), respectively.

3.3. Sensitivity analyses

The estimations of the association between the use of echocardiography and survival in ICU and at one year, adjusted by center (sensitivity analysis 1), including patients at centers where echocardiography was not available (sensitivity analysis 2), and restricting the Echocardiography group to those patients where the echocardiography was

performed within 24 h of ICU admission (sensitivity analysis 3), were similar to the results obtained in the main analysis (Fig. 2).

3.4. Subgroup analysis

Fig. 3 shows that although the interaction between etiology and echocardiography was not statistically significant for either ICU mortality (interaction $p = 0.075$) or one-year all-cause mortality (interaction $p = 0.088$), there is some suggestion that among patients admitted to ICU for cardiac disease, those managed with early echocardiography had a lower risk of in ICU [adjusted OR 0.48 (95% CI 0.24–0.93) $p = 0.031$] and one-year [adjusted HR 0.65 (95% CI 0.43–0.98) $p = 0.042$] mortality. Of note, there was no significant association between early echocardiography and one-year all-cause mortality in sepsis patients [adjusted HR 1.21 (95% CI 0.83–1.76) $p = 0.31$] (Fig. S1). The rest of the selected variables examined for interaction did not influence the association of echocardiography with one-year all-cause mortality (Fig. S1).

4. Discussion

In the present study, echocardiography showed marked alteration in heart contraction in ICU patients admitted for cardiac disease. However, despite better diagnosis, our study did not show that the use of echocardiography by the treating physician soon after ICU admission was associated with benefits on short- and long-term survival in ICU patients. To the best of our knowledge, this is a unique study assessing non-invasive cardiac hemodynamics in a large cohort of ICU patients. Our study shows that one-quarter of ICU patients were managed with echocardiography during the initial days of ICU stay. In addition, it showed that echocardiography, when performed, may help to determine the cause (s) of ICU admission. Indeed, hemodynamics was markedly altered in ICU patients admitted with cardiac cause compared to any other cause of ICU admission. We hypothesized that performing echocardiography in ICU patients is likely to help physicians choose the appropriate therapies and may also have an impact on survival. However, our study failed to demonstrate an association between echocardiography and outcome in a large ICU cohort. Few studies examined the association between the use of echocardiography and outcome in ICU settings, and only 3 of them studied ICU patients exclusively, although with selected diseases [17,23,24]. Our results diverge from those of the randomized study by Wang et al. [23] performed in 128 patients with cardiogenic pulmonary edema. The authors showed an association between the use of TTE and a reduced length of ICU stay; in addition, ICU mortality was also lower in the TTE group, though this difference was not statistically significant. Our results are in accordance with those of the randomized monocentric trial carried out by Merz et al. [24] in 545 circulatory shock patients, in whom no change in survival was observed when

Table 2
Echocardiographic parameters in the Echocardiography group within etiologies.

	Cardiac disease <i>n</i> = 126	Sepsis <i>n</i> = 83	Neurological disorder <i>n</i> = 43	Respiratory failure <i>n</i> = 76	Other <i>n</i> = 44	<i>p</i> value
LVEF (%)	40 [31–58]	55 [41–70]	57 [39–68]	55 [40–66]	55 [40–66]	<0.001
E/A ratio	1.1 [0.8–1.6]	1.2 [0.9–1.5]	1.1 [0.8–1.4]	1.0 [0.8–1.4]	1.1 [0.9–1.6]	0.85
Lateral E/e' ratio	7.8 [6.4–11.4]	8.3 [6.5–10.7]	7.2 [5.8–9.7]	7.1 [5.9–10.0]	6.3 [4.3–8.3]	0.039
Left atrial diameter (mm)	37 [31–43]	36 [31–42]	33 [30–37]	36 [32–42]	40 [34–47]	0.014
Cardiac output (L/min)	4.2 [3.2–5.7]	4.9 [3.8–6.3]	5.1 [4.1–6.3]	5.9 [4.6–7.0]	5.7 [3.7–7.9]	<0.001
RVDd (mm)	40 [35–45]	42 [34–48]	36 [34–42]	41 [35–46]	41 [34–44]	0.20
TRΔPG (mmHg)	28 [24–37]	26 [24–33]	26 [17–30]	35 [27–43]	25 [20–42]	0.10
TAPSE (mm)	18 [16–21]	20 [17–24]	21 [15–22]	18 [17–20]	24 [23–25]	0.074
IVC max diameter (mm)	20 [17–24]	19 [16–22]	18 [15–23]	20 [18–25]	16 [12–22]	0.096
Distensibility index of IVC (%)	22 [9–42]	18 [11–39]	29 [17–58]	19 [12–35]	31 [8–83]	0.64

Data are presented as the median [interquartile range].

A, peak velocity of late diastolic transmitral flow; E, peak velocity of early diastolic transmitral flow; e', peak velocity of early diastolic mitral annular motion as determined by pulsed wave Doppler; ICU, intensive care unit; IVC, inferior vena cava; LVEF: left ventricular ejection fraction, RVDd, Right ventricular dimension at end-diastole, TAPSE, tricuspid annular plane systolic excursion, TRΔPG transtricuspid pressure gradient.

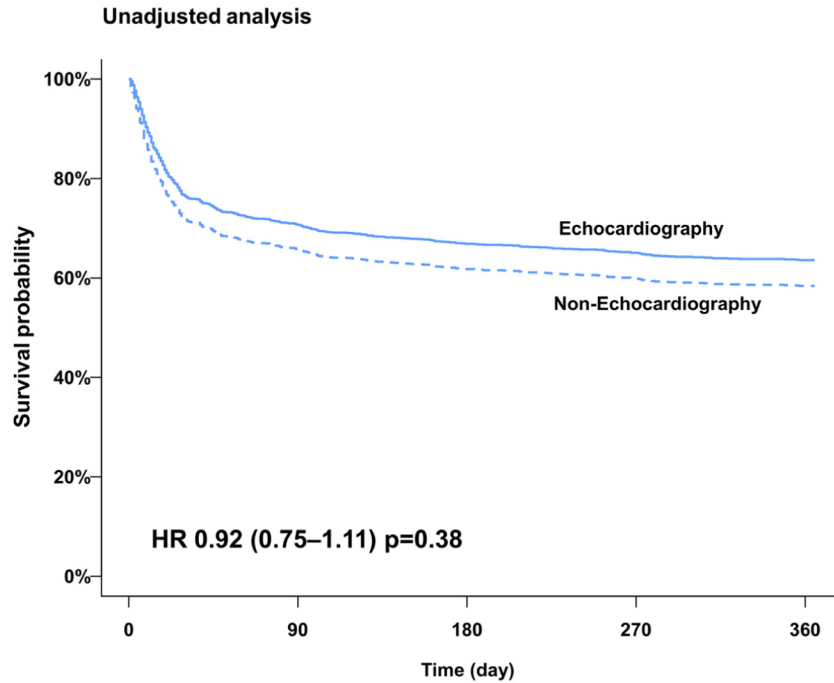


Fig. 1. Kaplan-Meier curve for one-year all-cause mortality in patients with and without early echocardiography by the treating physician. HR, hazard ratio.

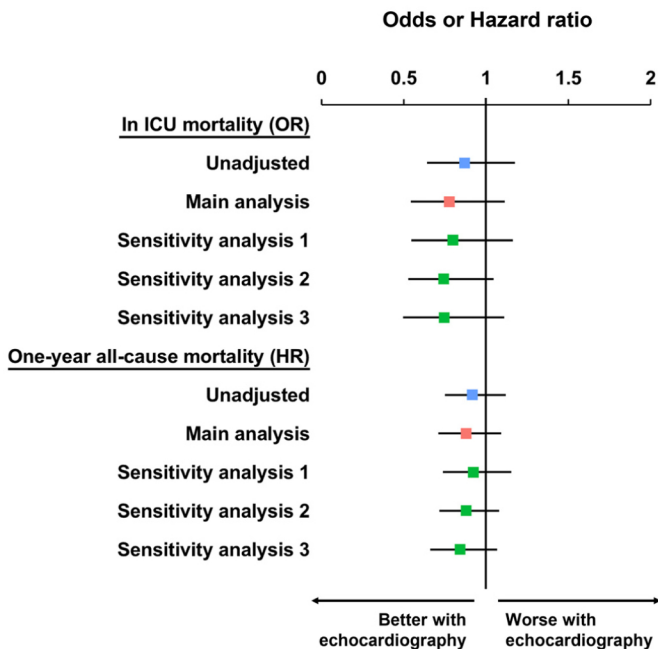


Fig. 2. Impact of early echocardiography on adjusted in ICU and one-year all-cause mortality.

The main analysis was performed after adjustment for covariates associated with ICU-mortality and one-year all-cause mortality in the multivariable model. Sensitivity analyses were performed by recalculating outcomes in three different ways: sensitivity analysis 1) multivariable-adjusted Cox regression analysis was repeated after adding adjustment by center (analysis on 1359 patients); sensitivity analysis 2) multivariable-adjusted Cox regression analysis was repeated without excluding patients in centers where echocardiography was not available in ICU (analysis on 2059 patients); 3) multivariable-adjusted Cox regression analysis was repeated, restricting the Echocardiography group to those patients where the echocardiography was performed within 24 h of ICU admission (analysis on 1375 patients).

HR, hazard ratio; ICU, intensive care unit; OR, odds ratio.

continuous single-use transesophageal echocardiography was used. Finally, when looking at subgroup analyses by cause(s) of admission, we found no significant interaction. However, our results on the subgroup of septic patients were divergent from the analysis of Feng et al. performed in patients included in the MIMIC-III cohort [17] that reported a benefit in 28-day mortality of patients with sepsis admitted to ICU when TTE was used. In our particular subgroup of FROG-ICU patients with sepsis, we did not observe such a benefit in one-year all-cause mortality. However, due to different design characteristics, our septic patients were mostly in shock, and those from MIMIC-III were mostly not in shock, as demonstrated by the higher rates of mechanical ventilation (94% vs. 53%) and vasopressor use (88% vs. 32%) observed in our study. Hence, in our study, echocardiography was performed in more severe septic shock patients who were possibly already in multiple organ failure and for whom hemodynamic management alone had fewer chances to influence outcomes. Another interesting exploratory analysis showed survival benefit for ICU patients with cardiac disease in whom echocardiography was performed early after ICU admission by the physician in charge. Our results likely highlight the beneficial role of putting diagnostic tools and therapeutic arsenal into the same hands. Effectively, this might shorten the time from hemodynamic assessment to therapeutic actions. Furthermore, echocardiography that includes measures of CO and cardiac filling pressures, predicting volume responsiveness, and monitoring the initial effects of therapeutic interventions, may be helpful in picking the most appropriate hemodynamic therapies. The latter include starting or stopping vasopressors or inotropes or fluid. Indeed, though those actions may be beneficial to ICU patients, several recent reports suggest a marked association between inappropriate use of vasopressor, inotrope and/or volume loading, and mortality [25-29]. As echocardiography is mostly focused on exploring heart function, it is foreseeable that the best benefits will be seen for diseases where the heart plays a significant role. In fact, the ESC, ESICM, and AHA guidelines [12-14] recommend that echocardiography should be performed at admission in patients with suspected circulatory shock or unstable acute heart failure.

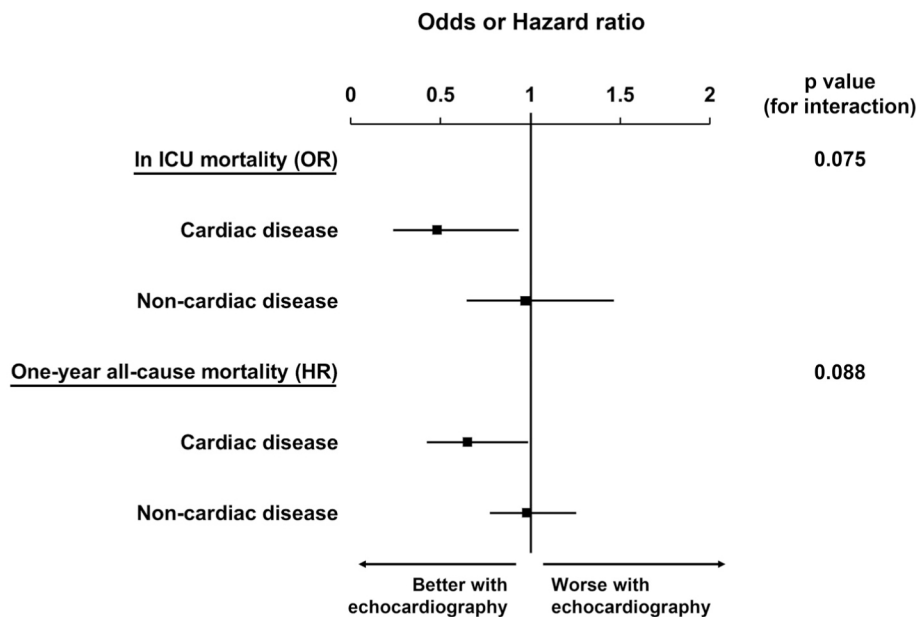


Fig. 3. Subgroup analysis for the impact of early echocardiography on adjusted in ICU and one-year all-cause mortality according to etiology. HR, hazard ratio; ICU, intensive care unit; OR, odds ratio.

4.1. Limitations

The present study has several limitations. Firstly, it was a non-randomized study. The observational nature of the data prevents confirming causality. The data, however, do not suggest any harm and provide solid information for further interventional randomized controlled trials. Secondly, echocardiography offers a non-continuous assessment, even if it is often performed repeatedly in ICU patients. However, in the present study, we did not examine the number of echocardiographic studies performed during the ICU stay. Therefore, it is not yet clear whether repeated ultrasound examinations were performed or not and whether this would influence the results. In addition, it is also unclear why the treating physician performed the echocardiography (for diagnosis, to assess the cause of hypotension, for fluid responsiveness assessment, etc.). Thirdly, echocardiography was performed later in some patients in the Non-Echocardiography group, and if echocardiography was beneficial, the results may have been biased towards no difference. Fourthly, some patients in Non-Echocardiography group received early hemodynamic monitoring device instead of Echocardiography. In that case, there is a possibility that the Non-Echocardiography group may have benefited from the device, and the effect of the echocardiography may be underestimated. In fact, ICU stay was shorter in the Echocardiography group when evaluated by excluding patients who used the device from the Non-Echocardiography group. Fifthly, the recently published the PRICES recommendation was designed for standardized reporting of critical care echocardiography studies [30]. Since the current study was conducted prior to this publication, the echocardiography was not performed according to these recommendations. Therefore, future studies following these recommendations are needed to evaluate the effects of echocardiography in ICU patients. Finally, among the patients in the Echocardiography group, several parameters were recorded at echocardiographic examination, though we did not examine the type or number of parameters that had the greatest prognostic impact.

5. Conclusion

The present study suggests that in critically ill patients admitted to the ICU, early echocardiography by treating physicians was not associated with short- or long-term survival. When looking at subgroups,

early echocardiography improved survival in ICU patients admitted for cardiac disease.

Ethics approval and consent to participate

The study was conducted in France and Belgium in accordance with Good Clinical Practice (Declaration of Helsinki 2002) and Ethical Committee approvals (Comité de Protection des Personnes—Ile de France IV, IRB no. 00003835 and Commission d'éthique biomédicale hospitalo-facultaire de l'hôpital de Louvain, IRB no. B403201213352). It is registered on [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT01367093). Patients were included from August 2011 to June 2013.

Consent for publication

Not applicable.

Availability of data and material

Prof. Mebazaa and Dr. Gayat had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Credit authorship contribution statement

Koji Takagi: Conceptualization, Methodology, Software, Formal analysis, Writing – original draft, Visualization. **Eiichi Akiyama:** Conceptualization, Methodology, Resources, Data curation, Writing – review & editing. **Alexis Paternot:** Data curation. **Ôscar Miró:** Validation, Writing – review & editing, Visualization. **Cyril Charron:** Data curation. **Etienne Gayat:** Data curation, Writing – review & editing, Project administration.

Nicolas Deye: Data curation. **Alain Cariou:** Data curation, Writing – review & editing. **Xavier Monnet:** Data curation. **Samir Jaber:** Data curation. **Bertrand Guidet:** Data curation. **Charles Damoiseil:** Data curation. **Romain Barthélémy:** Data curation. **Elie Azoulay:** Data curation. **Antoine Kimmoun:** Validation, Writing – review & editing, Supervision. **Marie-Céline Fournier:** Investigation, Resources, Data curation. **Bernard Cholley:** Data curation, Writing – review & editing. **Christopher Edwards:** Software, Formal analysis, Visualization. **Beth A. Davison:** Validation, Formal analysis, Writing – review & editing, Supervision. **Gad Cotter:** Validation, Writing – review & editing, Supervision. **Antoine Vieillard-Baron:** Conceptualization, Methodology, Validation, Investigation, Data curation, Writing – review & editing, Supervision, Project administration. **Alexandre Mebazaa:** Conceptualization, Methodology, Validation, Investigation, Data curation, Writing – review & editing, Supervision, Project administration.

Declaration of Competing Interest

KT received speaker's honoraria from Otsuka, Sumitomo Dainippon, AstraZeneca, and Bayer and consultancy fees from Terumo. **AK** received speaker's honoraria from Baxter, MSD, Gilead. **EG** received research grant from Spingotec and consultancy fees from Magnisense and Roche Diagnostics. **CE** is an employee of Momentum Research who received research grants from Abbott Laboratories, Amgen, Celyad, Cirius Therapeutics, Roche Diagnostics, Sanofi, and Windtree Therapeutics Inc. **BD** is an employee of Momentum Research who received research grants from Abbott Laboratories, Amgen, Celyad, Cirius Therapeutics, Roche Diagnostics, Sanofi, and Windtree Therapeutics Inc. **GC** is an employee of Momentum Research who received research grants from Abbott Laboratories, Amgen, Celyad, Cirius Therapeutics, Roche Diagnostics, Sanofi, and Windtree Therapeutics Inc. **AV** declares research grant from GSK company. **AM** reports personal fees from Novartis, Orion, Roche, Servier, Sanofi, Otsuka, Philips, grants and personal fees from Adrenomed, Abbott, as well as grants from 4TEEN4.

The other authors declared no potential conflicts of interest with respect to the research authorship and/or publication of this article.

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References

- Vieillard-Baron A, Slama M, Cholley B, Janvier G, Vignon P. Echocardiography in the intensive care unit: from evolution to revolution? *Intensive Care Med.* 2008;34:243–9. <https://doi.org/10.1007/s00134-007-0923-5>.
- Vignon P, Mentec H, Terre S, Gastinne H, Gueret P, Lemaire F. Diagnostic accuracy and therapeutic impact of transthoracic and transesophageal echocardiography in mechanically ventilated patients in the ICU. *Chest.* 1994;106:1829–34. <https://doi.org/10.1378/chest.106.6.1829>.
- Orme RML, Oram MP, McKinstry CE. Impact of echocardiography on patient management in the intensive care unit: an audit of district general hospital practice. *Br J Anaesth.* 2009;102:340–4. <https://doi.org/10.1093/bja/aen378>.
- Stanko LK, Jacobsohn E, Tam JW, De Wet CJ, Avidan M. Transthoracic echocardiography: impact on diagnosis and management in tertiary care intensive care units. *Anaesth Intensive Care.* 2005;33:492–6. <https://doi.org/10.1177/0310057x0503300411>.
- Tam JW, Nichol J, MacDiarmid AL, Lazarow N, Wolfe K. What is the real clinical utility of echocardiography? A prospective observational study. *J Am Soc Echocardiogr.* 1999;12:689–97. [https://doi.org/10.1016/S0894-7317\(99\)70018-0](https://doi.org/10.1016/S0894-7317(99)70018-0).
- Sanfilippo F, Di Falco D, Noto A, Santonocito C, Morelli A, Bignami E, et al. Association of weaning failure from mechanical ventilation with transthoracic echocardiography parameters: a systematic review and meta-analysis. *Br J Anaesth.* 2021;126:319–30. <https://doi.org/10.1016/j.bja.2020.07.059>.
- Sanfilippo F, Corredor C, Fletcher N, Landesberg G, Benedetto U, Foex P, et al. Diastolic dysfunction and mortality in septic patients: a systematic review and meta-analysis. *Intensive Care Med.* 2015;41:1004–13. <https://doi.org/10.1007/S00134-015-3748-7>.
- Sanfilippo F, Corredor C, Arcadipane A, Landesberg G, Vieillard-Baron A, Cecconi M, et al. Tissue Doppler assessment of diastolic function and relationship with mortality in critically ill septic patients: a systematic review and meta-analysis. *Br J Anaesth.* 2017;119:583–94. <https://doi.org/10.1093/BJA/AEX254>.
- Sanfilippo F, Corredor C, Fletcher N, Tritapepe L, Lorini FL, Arcadipane A, et al. Left ventricular systolic function evaluated by strain echocardiography and relationship with mortality in patients with severe sepsis or septic shock: a systematic review and meta-analysis. *Critical Care (London, England).* 2018;22. <https://doi.org/10.1186/S13054-018-2113-Y>.
- Huang SJ, Nalos M, McLean AS. Is early ventricular dysfunction or dilatation associated with lower mortality rate in adult severe sepsis and septic shock? A meta-analysis. *Critical Care (London, England).* 2013;17. <https://doi.org/10.1186/CC12741>.
- Sanfilippo F, Huang S, Messina A, Franchi F, Oliveri F, Vieillard-Baron A, et al. Systolic dysfunction as evaluated by tissue Doppler imaging echocardiography and mortality in septic patients: a systematic review and meta-analysis. *J Crit Care.* 2021;62:256–64. <https://doi.org/10.1016/j.jcrc.2020.12.026>.
- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution. *Eur J Heart Fail.* 2016;18:891–975. <https://doi.org/10.1002/ehf.592>.
- Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Medicine.* 2014;40:1795–815. <https://doi.org/10.1007/s00134-014-3525-z>.
- Van Diepen S, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, et al. Contemporary Management of Cardiogenic Shock: a scientific statement from the American Heart Association. *Circulation.* 2017;136:e232–68. <https://doi.org/10.1161/CIR.0000000000000525>.
- Pack QR, Priya A, Lagu T, Pekow PS, Schilling JP, Hiser WL, et al. Association between inpatient echocardiography use and outcomes in adult patients with acute myocardial infarction. *JAMA Intern Med.* 2019;179:1176–85. <https://doi.org/10.1001/jamainternmed.2019.1051>.
- Papalos A, Narula J, Bavishi C, Chaudhry FA, Sengupta PP. U.S. Hospital use of echocardiography: insights from the Nationwide inpatient sample. *J Am Coll Cardiol.* 2016;67:502–11. <https://doi.org/10.1016/j.jacc.2015.10.090>.
- Feng M, McSparron J, Kien DT, Stone DJ, Roberts DH, Schwartzstein RM, et al. Transthoracic echocardiography and mortality in sepsis: analysis of the MIMIC-III database. *Intensive Care Med.* 2018;44:884–92. <https://doi.org/10.1007/s00134-018-5208-7>.
- Gayat E, Cariou A, Deye N, Vieillard-Baron A, Jaber S, Damoiseil C, et al. Determinants of long-term outcome in ICU survivors: results from the FROG-ICU study. *Crit Care.* 2018;22. <https://doi.org/10.1186/s13054-017-1922-8>.
- Mebazaa A, Casadio MC, Azoulay E, Guidet B, Jaber S, Levy B, et al. Post-ICU discharge and outcome: rationale and methods of the the French and euROpean outcome reGistry in intensive care units (FROG-ICU) observational study. *BMC Anesthesiol.* 2015;15. <https://doi.org/10.1186/s12871-015-0129-2>.
- Barbier C, Loubières Y, Schmit C, Hayon J, Ricôme JL, Jardin F, et al. Respiratory changes in inferior vena cava diameter are helpful in predicting fluid responsiveness in ventilated septic patients. *Intensive Care Med.* 2004;30:1740–6. <https://doi.org/10.1007/S00134-004-2259-8>.
- van Buuren S, Groothuis-Oudshoorn K. Mice: multivariate imputation by chained equations in R. *J Stat Softw.* 2011;45:1–67. <https://doi.org/10.18637/jss.v045.i03>.
- Frank E. Harrell Jr. rms: Regression Modeling Strategies. R package version 6.1–0. <https://cran.r-project.org/package=rms>; 2020. [Accessed 25 January 2021].
- Wang XT, Liu DW, Zhang HM, Chai WZ. Integrated cardiopulmonary sonography: a useful tool for assessment of acute pulmonary edema in the intensive care unit. *J Ultrasound Med.* 2014;33:1231–9. <https://doi.org/10.7863/ultra.33.7.1231>.
- Merz TM, Cioccarelli L, Frey PM, Bloch A, Berger D, Zante B, et al. Continual hemodynamic monitoring with a single-use transesophageal echocardiography probe in critically ill patients with shock: a randomized controlled clinical trial. *Intensive Care Med.* 2019;45:1093–102. <https://doi.org/10.1007/s00134-019-05670-6>.
- Levy B, Clere-Jehl R, Legras A, Morichau-Beauchant T, Leone M, Frederique G, et al. Epinephrine versus norepinephrine for cardiogenic shock after acute myocardial infarction. *J Am Coll Cardiol.* 2018;72:173–82. <https://doi.org/10.1016/j.jacc.2018.04.051>.
- Mebazaa A, Motiejunaite J, Gayat E, Crespo-Leiro MG, Lund LH, Maggioni AP, et al. Long-term safety of intravenous cardiovascular agents in acute heart failure: results from the European Society of Cardiology Heart Failure Long-Term Registry. *Eur J Heart Fail.* 2018;20:332–41. <https://doi.org/10.1002/ehf.991>.
- Scheeren TWL, Bakker J, De Backer D, Annane D, Asfar P, Boerma EC, et al. Current use of vasopressors in septic shock. *Ann Intensive Care.* 2019;9. <https://doi.org/10.1186/s13613-019-0498-7>.
- Vincent JL, Weil MH. Fluid challenge revisited. *Crit Care Med.* 2006;34:1333–7. <https://doi.org/10.1097/01.CCM.0000214677.76535.A5>.
- Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, DeBoisblanc B, et al. Comparison of two fluid-management strategies in acute lung injury. *New England Journal of Medicine.* 2006;354:2564–75. <https://doi.org/10.1056/NEJMoa062200>.
- Sanfilippo F, Huang S, Herpain A, Balik M, Chew MS, Clau-Terré F, et al. The PRICES statement: an ESCIM expert consensus on methodology for conducting and reporting critical care echocardiography research studies. *Intensive Care Med.* 2021;47:1–13. <https://doi.org/10.1007/S00134-020-06262-5>.