Assessing the Association Between Cardiovascular Acoustic Biomarkers and Heart Failure: A Systematic Literature Review

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Data extraction

- Articles were extracted using Microsoft Excel for the following information:
  - Publication information: study identification, publication type, author, year, and title;
  - Study characteristics: study type, objectives, and country;
  - Population characteristics: study population, subgroup definition, method of assessing population diagnoses, age, sex, medical history, and other health-related biomarkers;
  - Cardiovascular acoustic biomarker (CAB)-related characteristics: measures, definition, and method of assessment;
  - Outcomes of interest: predictive data, correlations, incidence of outcomes, associations between CABs and clinical, humanistic, and economic outcomes.
- Only 3 studies were found to potentially have a high risk of bias as determined by the Joanna Briggs Institute (JBI) appraisal tool with remaining studies found to have a low risk of bias (**Supplemental Table S6**)

Supplemental Table S1. Studies reporting S3 detection and monitoring of HF

Study	Key results
Wang and Lam et al. 2013[10]	• S3 score and intensity were statistically significantly increased in patients with HFrEF compared with those with HFnEF S3 intensity (P < 0.001) ○ HFrEF: 0.66 ± 0.54 ○ HFnEF: 0.54 ± 0.57 S3 score (P < 0.001) ○ HFrEF: 4.63 ± 2.09 ○ HFnEF: 3.31 ± 1.67
Wang and Fang et al. 2013[11]	• S3 score was statistically significantly greater in patients with more severe (EF ≤ 35%) HF (P = 0.002) ○ Patients with 35% < EF < 50%: 4.27 ± 2.09 ○ Patients with EF ≤ 35%: 5.44 ± 2.12 ○ Patients with NRDD: 3.95 ± 1.90 ○ Patients with RDD: 5.86 ± 2.04 • Patients with NRDD had statistically significantly lower S3 scores compared with patients with RDD (P < 0.001)
Calò et al. 2020[12]	• S3 amplitude (mG, mean ± SD) statistically significantly increased in patients with potential worsening of HF (unpaired comparison, P < 0.05) ○ Patients without alerts and with HeartLogic index < 16: 0.9 ± 0.3 ○ Patients with alerts and with HeartLogic index > 16: 1.3 ± 0.3 • S3 > 0.9 mG detected a restrictive filling pattern with a sensitivity of 85% (95% CI: 72%–93%) and a specificity of 82% (95% CI: 75%–88%)
Siejko et al. 2013[13]	• S3 amplitude (mG, mean ± SD) was statistically significantly increased in patients with HF (P < 0.001) ○ HF group: 3.4 ± 2.4 ○ Non-HF group: 1.7 ± 0.40 • Moderate to loud auscultated S3 was more prevalent in the combined NYHA class III/IV subgroup compared to NYHA class II subgroup (79% vs 44%, P = 0.05)
Dao et al. 2022[14]	• S3 had moderate predictive value in the screening of HF with combined sensitivity of 0.23 (95% CI: 0.15–0.33) and specificity of 0.94 (95% CI: 0.82–0.98) • S3 had lower sensitivity in diagnosing HF compared to LVEF
Selvaraj et al. 2019[15]	• Absence of S3 was associated with a mean of 3 (95% CI, 4.5–5.7) point increase in KCCQ-OSS (P < 0.001) • S3 frequency increased in patients with HF who also showed increased signs of HF ○ Patients with 1 vs 0 signs; HR: 1.77 (95% CI: 1.59–1.96) ○ Patients with 2 vs 0 signs; HR: 2.61 (95% CI: 2.24–3.03) ○ Patients with 3 vs 0 signs; HR: 4.22 (95% CI: 3.45–5.16) ○ Patients with 4 vs 0 signs; HR: 11.88 (95% CI: 8.17–17.29)

CI, confidence interval; EF, ejection fraction;HF, heart failure; HFnEF, HF with normal ejection fraction; HFrEF, HF with reduced ejection fraction; HR, hazard ratio; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score; LVEF, left ventricular ejection fraction; mG, milligravity; NRDD, non-restrictive diastolic dysfunction; NYHA, New York Heart Association; RDD, restrictive diastolic dysfunction; S3, third heart sound; SD, standard deviation.

Supplemental Table S2. Studies reporting relationships between S3 amplitude and HF outcomes

Study	Key results

Gardner and Capodilupo et al. 2021[16]	• No statistically significant changes were observed in S3 amplitude in patients with COVID-19 or pneumonia compared with the known changes in patients with decompensated HF
	• A statistically significant increase was observed in S3 amplitude (mG, mean ± SD) in patients prior to a cardiac event ($P < 0.001$)
	  ○ Baseline: 1.22 ± 0.39
	  ○ Pre-event: 1.34 ± 0.45

Gardner and Thakur et al. 2021[17]	• S3 amplitude (mG, mean ± SD) was statistically significantly higher prior to a cardiac event in patients with HFE than those without HFE ($P < 0.001$)
	  ○ Patients with a HFE: 1.13 ± 0.36
	  ○ Patients without any HFEs: 0.91 ± 0.30
	• S3 amplitude (mG, mean ± SD) statistically significantly differed between baseline vs pre-event ($P < 0.001$), pre-event vs day of the event ($P = 0.014$), and day of the event vs recovery ($P < 0.001$)
	  ○ Baseline: 1.24 ± 0.39
	  ○ Pre-event: 1.34 ± 0.42
	  ○ Day of event: 1.41 ± 0.52
	  ○ Recovery: 1.27 ± 0.43

Ahmed et al. 2022[18]	• S3 magnitude measured in patients with HF prior to discharge was statistically significantly greater in readmitted patients than in those who were not readmitted ($P < 0.0001$)
	  ○ Readmitted patients: 0.28
	  ○ Not readmitted patients: 0.24

Chang et al. 2015[19]	• Patients with HF events had statistically significantly lesser 24 h and nighttime S3 strength compared to patients without events
	S3 strength, 24 h ($P = 0.042$)
	  ○ Patients without events: 4.0 ± 1.8
	  ○ Patients with events: 3.3 ± 1.1
	S3 strength, nighttime, ($P = 0.043$)
	  ○ Patients without events: 4.1 ± 1.9
	  ○ Patients with events: 3.4 ± 1.2

Cao et al. 2020[20]	• Device-measured S3 had superior prognostic value to predict future HFEs compared with auscultation
	• Device-measured S3 (mG, median [IQR]) was statistically significantly different between patients with HFE vs those without HFE ($P < 0.0001$)
	  ○ Patients without HFE: 0.85 (0.70–1.01)
	  ○ Patients with HFE: 1.03 (0.85–1.37)
	• No differences were observed in the numbers of auscultated S3 between patients with HFE vs without HFE ($P = 0.69$)
	• Number of patients with none/low/medium/loud S3:
	  ○ Patients without HFE: 621/52/15/1
	  ○ Patients with HFE: 76/9/3/0

HF, heart failure; HFE, heart failure event; IQR, interquartile range; mG, milligravity; S3, third heart sound; SD, standard deviation.

Supplemental Table S3. Studies reporting relationships between S3 presence and HF outcomes

Study	Key results
Chang et al. 2015[19]	• Patients with events had statistically significantly less frequent nighttime S3 detection (*P* = 0.047) o Patients without events: 29.7 o Patients with events: 10.5
Gurjão et al. 2022[21]	• Presence of S3 during hospital admission was a statistically significant predictor of mortality among patients with HF (*P* = 0.0001) o Patients died with detectable S3: 33.33% o Patients died without detectable S3: 5.42%
Jering et al. 2021[22]	• More patients in the high-burden (≥ 3 signs and symptoms of HF) group had S3 detected at randomization compared to those in the low-burden (≤ 2 signs and symptoms of HF) group (*P* < 0.001) o High-burden group with S3 detection (n = 1772): 87 o Low-burden group with S3 detection (n = 2953): 23 • S3 was not independently associated with total hospitalizations due to HF, all-cause, or cardiovascular death
Negi et al. 2014[23]	• Patients with S3 presence on admission had statistically significantly higher readmission rates than those without S3 (*P* = 0.013); HR (95% CI): 2.077 (1.165–3.700) • S3 was also associated with troponin T > 0.10 ng/mL on discharge (*P* = 0.018), OR (95% CI): 2.939 (1.206–7.159)
Minami et al. 2015[24]	• S3 detection on admission was independently associated with increased in-hospital all-cause death and cardiovascular death in patients with HF o All-cause mortality, adjusted OR (95% CI): 1.69 (1.19–2.41; *P* = 0.003) o Cardiac mortality, adjusted OR (95% CI): 1.66 (1.08–2.54; *P* = 0.020)
Wang et al. 2016[25]	• Patients with S3 scores ≥ 4 had statistically significantly lower survival (56.8% vs 68.6%, Log-rank χ = 10.58) than those with lower S3 scores (*P* = 0.001)

CI, confidence interval; HF, Heart failure; HR, hazard ratio; OR, odds ratio; S3, third heart sound.

Supplemental Table S4. Studies reporting EMAT relationships between EMAT and HF

Study	Key results
Wang and Lam et al. 2013[10]	• EMAT/RR was the superior acoustic cardiographic parameter for detecting HFnEF (*P* < 0.001) with EMAT/RR > 11.54% yielding 55% sensitivity and 90% specificity o Patients with HFrEF (EF < 50%): 15.1% ± 3.65% o Patients with HFnEF (EF ≥ 50%): 12.21% ± 3.05%
Wang and Fang et al. 2013[11]	• EMAT% was statistically significantly longer in patients with severely impaired EF (EF ≤ 35%) vs patients with moderately impaired EF (35% < EF < 50%) (*P* = 0.036) o Patients with moderately impaired EF: 14.57 ± 4% o Patients with severely impaired EF: 15.94 ± 3.26%
Zhang and Zhang. 2022[27]	• EMAT% was a useful biomarker for the diagnosis of HF with LVEF < 50% • EMAT% > 12.1% had 81% sensitivity and 82% specificity for the diagnosis of LVEF < 50%
Li et al. 2020[28]	• EMAT ≥ 104 ms to determine EF < 50% resulted in a sensitivity of 92.1% and specificity of 92.0% • EMAT (ms, mean ± SD) was statistically significantly higher in patients with dLVEF compared with control group (*P* < 0.001) o Patients with dLVEF: 159.82 ± 83 o Control group: 91.58 ± 28
Trabelsi et al. 2020[29]	• EMAT (ms, mean ± SD) was statistically significantly higher in patients with HF vs those without HF (*P* < 0.001) o Patients with HF: 116 ± 25 o Patients without HF: 100 ± 23 • EMAT (ms, mean ± SD) was significantly higher in patients with HFrEF vs HFpEF (*P* = 0.028) o HFrEF: 128 ± 21 o HFpEF: 113 ± 30

dLVEF, decreased LVEF; EF, ejection fraction; EMAT, electromechanical activation time; EMATc, cardiac cycle time-corrected EMAT; EMAT/RR, EMAT normalized to heart rate; EMAT%, normalized electromechanical activation time; HF, heart failure; HFnEF, HF with normal ejection fraction; HRpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; LVEF; left ventricular ejection fraction; ms, millisecond; SD, standard deviation.

Supplemental Table S5. Studies reporting relationships between EMAT and HF outcomes

Study	Key results

Chang et al. 2015[19]	• Predischarge nighttime EMAT statistically significantly predicted postdischarge events (adjusted nighttime EMAT, HR per 1 SD [95% CI]: 1.33 [1.05–1.69], *P* < 0.05)
	• Nighttime EMAT, ms (*P* = 0.007)
	  ○ Patients without events: 103.0 ± 13.8
	  ○ Patients with events: 114.3 ± 20.5

Wang et al. 2016[25]	• EMAT% predicted cardiac mortality
	  ○ Univariate analysis, HR (95% CI): 1.093 (1.045–1.143; *P* < 0.001)
	  ○ Multivariate analysis, HR (95% CI): 1.106 (1.053–1.162; *P* < 0.001)

Zhang and Zhang. 2022[27]	• EMAT% > 12.1% had 81% sensitivity and 82% specificity for the diagnosis of LVEF < 50% ○ Patients with EMAT% > 12.1% had a higher occurrence of MACE, compared with patients with EMAT ≤ 12.1% group in post-STEMI patients (36.54% vs 8.11%; *P* < 0.001)

Chang et al. 2020[30]	• Nighttime EMAT% was a statistically significant predictor of hospitalization due to HF or death from any cause (primary composite event)
	  ○ Nighttime EMAT% for primary composite event, adjusted HR (95% CI): 1.186 (1.020–1.377; *P* = 0.026)
	  ○ Nighttime EMAT% for recurrent composite events adjusted HR (95% CI): 1.267 (1.104–1.456; *P* < 0.001)

Zhang and Liu 2022[31]	• EMATc > 15% was an independent risk factor for cardiogenic death ○ 8/14 (51.7%) patients in the cardiogenic death group had a EMATc > 15% compared with 29/106 (27.4%) patients in the non-cardiogenic death group (*P* = 0.032) • HR (95% CI) for EMATc > 15% for cardiogenic death was 3.493 (1.021–11.95; *P* = 0.046)

Zhang and Liu 2020[32]	• EMATc > 13.8% measured at admission was an independent risk factor for MACE among hospitalized CHF patients; OR (95% CI): 6.578 (1.931–22.416; *P* = 0.003)
	• EMATc, median (IQR) was statistically significantly higher in patients with MACE compared with those without MACE (*P* < 0.001)
	  ○ Patients with MACE: 16.5 (14.0, 20.2)
	  ○ Patients without MACE: 12.7 (10.3, 15.0)

CHF, chronic HF; CI, confidence interval; EMAT, electromechanical activation time; EMATc, cardiac cycle time-corrected EMAT; EMAT%, normalized electromechanical activation time; HF, heart failure; HR, hazard ratio; IQR, interquartile range; LVEF, left ventricular ejection fraction; MACE, major cardiac adverse event; ms, millisecond; OR, odds ratio; STEMI, ST-elevated myocardial infarction.

Supplemental Table S6. Risk of bias conclusions for all included publications

First author	Study title	Year	Risk of bias
Zhang, WL	Evaluation of cardiac function and 30-day clinical outcome with synchronized analysis of phonocardiogram and electrocardiogram in patients with acute myocardial infarction	2022	High
Gardner, RS	Multiparameter diagnostic sensor measurements in heart failure patients presenting with SARS-CoV-2 infection	2021	High
Negi, S	Prognostic implication of physical signs of congestion in acute heart failure patients and its association with steady-state biomarker levels	2014	High
Jering, K	Burden of heart failure signs and symptoms, prognosis, and response to therapy	2021	Low
Sung, SH	Effect of acoustic cardiography-guided management on 1-year outcomes in patients with acute heart failure	2020	Low
Wang, S	Rapid bedside identification of high-risk population in heart failure with reduced ejection fraction by acoustic cardiography	2013	Low
Wang, S	Acoustic cardiography helps to identify heart failure and its phenotypes	2013	Low
Siejko, KZ	Feasibility of heart sounds measurements from an accelerometer within an ICD pulse generator	2013	Low
Selvaraj, S	Prognostic implications of congestion on physical examination among contemporary patients with heart failure and reduced ejection fraction: PARADIGM-HF	2019	Low
Zhang, J	Predictive value of electromechanical activation time for in-hospital major cardiac adverse events in heart failure patients	2020	Low
Sakai, C	Absent fourth heart sound as a marker of adverse events in hypertrophic cardiomyopathy with sinus rhythm	2021	Low
Erath, JW	Influence of decompensated heart failure on cardiac acoustic biomarkers: impact on early readmissions	2020	Low
Cao, M	Ambulatory monitoring of heart sounds via an implanted device is superior to auscultation for prediction of heart failure events	2020	Low
Ahmed, M	Assessment of heart sounds as predictors of rehospitalizations using a noninvasive multiple sensor monitoring device	2022	Low
Zhang, J	Cardiac cycle time-corrected electromechanical activation time greater than 15% is an independent risk factor for major adverse cardiovascular events in chronic heart failure outpatients.	2022	Low
Gurjão, F	The presence of the third heart sound as a predictor of mortality in patients with heart failure in a referral hospital in the North of Ceará	2022	Low
Boehmer, J	A multisensor algorithm predicts heart failure events in patients with implanted devices	2017	Low
Trabelsi, I	Value of systolic time intervals in the diagnosis of heart failure in emergency department patients with undifferentiated dyspnea.	2020	Low
Calò, L	ICD-measured heart sounds and their correlation with echocardiographic indexes of systolic and diastolic function	2020	Low
Minami, Y	Third heart sound in hospitalized patients with acute heart failure: insights from the ATTEND study	2015	Low
Chang, CC	Night-time electromechanical activation time, pulsatile hemodynamics, and discharge outcomes in patients with acute heart failure	2015	Low
Chang, HC	Nocturnal thoracic volume overload and post-discharge outcomes in patients hospitalized for acute heart failure	2020	Low
Li, XC	Evaluation of left ventricular systolic function using synchronized analysis of heart sounds and the electrocardiogram	2020	Low
Gardner, RS	Multiparameter diagnostic sensor measurements during clinically stable periods and worsening heart failure in ambulatory patients	2021	Low
Liu, Y	An automatic approach using ELM classifier for HFpEF identification based on heart sound characteristics	2019	Low
Capucci, A	Preliminary experience with the multisensor HeartLogic algorithm for heart failure monitoring: a retrospective case series report	2019	Low
Dao, L	A systemic review and meta-analysis comparing the ability of diagnostic of the third heart sound and left ventricular ejection fraction in heart failure	2022	Low
Wang, S	Prognostic value of acoustic cardiography in patients with chronic heart failure	2016	Low

Quality and bias assessment was completed by utilizing the JBI critical appraisal tools[33], and study-specific JBI risk of bias checklists were used for each study design.
ELM, extreme learning machine; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; ICD, implantable cardiac defibrillator; JBI, Joanna Briggs Institute.

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