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A cohort study evaluating myocardial work and right ventricle strain in sepsis in critical care

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The understanding of sepsis-related changes in myocardial function is evolving. This single-centre prospective observational cohort pilot study evaluated myoCardial work and Right ventricle Strain In Sepsis (CRiSIS) with 30-day mortality in critical care patients. Measurements were recorded for 32 patients on days 1 and 3 of admission: 22 (69%) survivors and 10 (31%) non-survivors at 30 days. Survivors demonstrated a higher global work efficiency (GWE; 94%, IQR 91–96%) compared to non-survivors (88.5%, IQR 85–92%; p = 0.02, BF_{10} = 1.44) on day 3. No significant differences in changes between day 1 and day 3 were observed in MW or RV FWS. Bayesian analysis supported a possible difference in global work index (GWI) and global constructive work (GCW) between survivors and non-survivors on day 1 and for global work index (GWI) on day 3. GWI, GCW, and GWE strongly correlated with left ventricle ejection fraction (LVEF) and global longitudinal strain (GLS), while the relationship with global wasted work (GWW) was weaker. To the best of our knowledge, this is the first study to investigate the role of MW in critically ill patients presenting with sepsis and suggests that it may be a valuable prognostic tool in this patient population.

Keywords Sepsis, Cardiac, Myocardial, Work, Strain, Mortality

Abbreviations

ATP	Adenosine triphosphate
AVC	Aortic valve closing
AVO	Aortic valve opening
BF	Bayes factor
FAO	Fatty acid oxidation
GCW	Global constructive work
GLS	Global longitudinal strain
GWE	Global work efficiency
GWI	Global work index
GWW	Global wasted work
ICC	Intraclass correlation coefficient
ISRCTN	International standard randomised controlled trial number
IQR	Interquartile range
IVC	Isovolumetric contraction
IVR	Isovolumetric relaxation
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MVC	Mitral valve closing
MVO	Mitral valve opening
MW	Myocardial work
NIBP	Non-invasive blood pressure
RV	Right ventricle
RV FWS	Right ventricular free wall strain
SD	Standard deviation
SOFA	Sequential organ failure assessment
STE	Speckle-tracking echocardiography
TTE	Transthoracic echocardiography

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In the UK, over 30% of critical care admissions are sepsis related[1]. Myocardial dysfunction is common in sepsis, affecting 25–50% of patients via systolic and/or diastolic impairment of the left ventricle (LV) and/or right ventricle (RV)[2]. Circulatory failure is a major contributor to sepsis-related mortality[3,4], but identifying reliable echocardiographic predictors of poor outcomes has been challenging as traditional LV and RV systolic function markers have not proved entirely effective at predicting mortality[5–7]. Conventional echocardiographic measures like LV ejection fraction (EF) are determined in part by afterload conditions and so may appear normal in septic patients with distributive shock even when intrinsic myocardial function is impaired. Novel echocardiographic techniques of myocardial work (MW) and right ventricle free wall strain (RV FWS) may offer more load-independent insight into cardiac dysfunction in sepsis and contribute to predicting outcomes in these patients. Additional insight into myocardial energy metabolism may be possible via MW derived indices, shining a light on possible explanatory physiological processes underpinning myocardial dysfunction in sepsis[8].

MW assessment is a novel echocardiographic technique that considers LV deformation as well as afterload[9]. It combines LV global longitudinal strain (GLS) measurements via Speckle Tracking Echocardiography (STE) with non-invasive blood pressure (NIBP) as a surrogate for LV pressure and afterload. This allows for a more accurate assessment of intrinsic LV function, potentially detecting subclinical disease[10]. MW has been validated as a non-invasive method for calculating LV pressure-strain loops, with strong correlation to invasive catheter methods[11]. MW assessment produces estimates for the global work index (GWI; mmHg %), global constructive work (GCW; mmHg %), global wasted work (GWW; mmHg %), and global work efficiency (GWE; %) as defined in our methods (also see Fig. 1). Research into MW derived indices has demonstrated correlation with hypertensive disease severity[10]; predicting all-cause mortality, need for transplant or mechanical support in patients with Heart Failure with reduced Ejection Fraction (HFrEF)[12]; predicting myocardial wall segment recovery following ST-Elevation Myocardial Infarction[13]; diagnostic and prognostic value in cardio-oncology, valvular disease, cardiomyopathies, and cardiac resynchronisation therapy[14–17]. Despite its crucial role in shock states, research on RV echocardiographic assessment is limited. Novel proprietary software now applies GLS to the RV, offering reduced load-dependence, better inter-rater reliability, and improved detection of regional and subclinical abnormalities[18]. RV FWS has been shown to outperform traditional RV echocardiographic measurements, predict mortality in pulmonary hypertension, tricuspid regurgitation and in COVID-19 patients requiring mechanical ventilation[19–21].

A literature review reveals no studies evaluating the feasibility, efficacy, or prognostic value of MW in critically ill patients presenting with sepsis, and limited research has been conducted on RV FWS in this population[21–23]. For RV FWS, an observational study, involving 60 patients with severe sepsis or septic shock, found that traditional echocardiographic markers poorly predicted outcomes, whereas RV FWS was associated with mortality[24]. As no specific data were available on the assessment of MW and minimal data on RV FWS in patients presenting with sepsis to critical care, the aims of our CRiSIS study were to

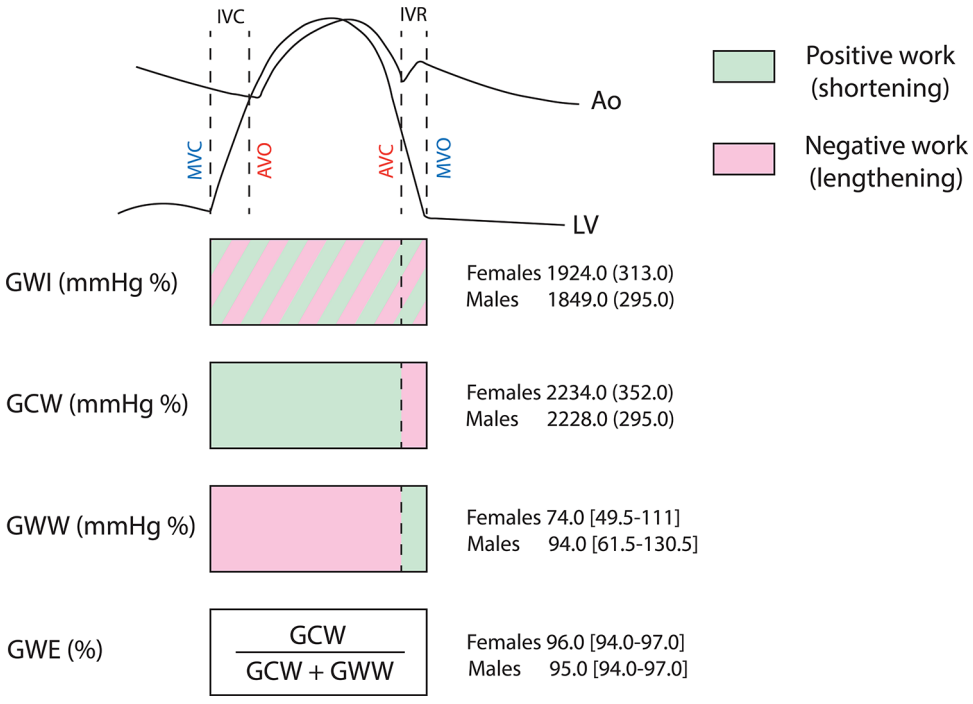

Fig. 1. Global work index (GWI); global constructive work (GCW); global wasted work (GWW); global work efficiency (GWE); *Ao* aorta, *LV* left ventricle; normal values presented as mean (SD) or median [IQR][31]. See text for details.

1. Investigate if MW and RV FWS measured on days 1 and 3 of admission are associated with 30-day mortality
2. Investigate if any association exists between the interval changes (i.e. the difference in measurements recorded on day 1 and day 3 of their admission) in MW and RV FWS on 30-day mortality
3. Assess if any differences exist on day 1 between male and female patients in MW and RV FWS
4. Provide insights into the degree to which myocardial work and RV FWS are associated with GLS and LVEF

Methods

Study design and ethical approval

We conducted a single centre prospective observational cohort pilot study between July 2021 and December 2023 in critical care patients presenting with sepsis admitted to the critical care unit at East Surrey Hospital, Surrey, United Kingdom. As a pilot study, we aimed to recruit either 50 patients or to the end of the study period, whichever came first.

Echocardiographic parameters collected adhered to the Preferred Reporting Items for Critical care Echocardiography Studies (PRICES) recommendations[25]. During the writing of this manuscript, we adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist[26]. This study was prospectively registered online at the International Standard Randomised Controlled Trial Number registry (ISRCTN23174569) and was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Informed consent was either obtained from patients prior to participating, or where the patient was incapacitated, informed consent was obtained from their next of kin. The study protocol was reviewed and approved by the London Bromley Research Ethics Committee (21/LO/0303).

Inclusion and exclusion criteria

We performed transthoracic echocardiography (TTE) examination on day 1 and day 3 of the admission in patients presenting with sepsis as defined by Sepsis-3[27]. Patients were excluded if less than 18 years old or had atrial fibrillation, suboptimal image quality, previous cardiac surgery, pregnancy, or severe valvular disease.

Measurements and outcomes

Clinical variables

We recorded patients age, sex, weight (kg), height (m), body mass index (BMI), body surface area (BSA; m^2), systolic (SBP) and diastolic blood pressure (DBP) using invasive arterial blood pressure monitoring, heart rate (HR), source of infection, dose of vasopressor (mcg/kg/min) and mode of ventilation (e.g. spontaneous or mechanical), and the Sequential Organ Failure Assessment (SOFA) score at time of TTE examination for each patient on day 1 and 3 of admission. In addition, if present, we recorded the following pre-morbid conditions: ischaemic heart disease (IHD), hypertension (HTN), heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), permanent pacemaker (PPM), chronic obstructive pulmonary disease (COPD), pulmonary hypertension (PHT), chronic kidney disease (CKD), and coronavirus disease (COVID-19).

Haematology and biochemical variables

For patients with more than one set of blood laboratory results in a 24 h period, we recorded lowest haemogoblin level (g/dL), lowest white blood cell count ($\times 10^9$/L), lowest platelet count ($\times 10^9$/L), lowest sodium plasma level (mmol/L), highest potassium plasma level (mmol/L), highest serum urea (mmol/L), highest creatinine (mmol/L), highest lactate (mmol/L), and highest bilirubin (mmol/L) on days 1 and 3 of admission. For patients with a single set of blood laboratory results, these variables were recorded according to the values obtained, as these were the only set available.

TTE examination

TTE examinations were performed by both the authors using either a GE S70 R2 or GE Vivid IQ ultrasound device (GE Chalfont St Giles, Buckinghamshire, Great Britain). Both authors are fully accredited by the British Society of Echocardiography in TTE. The TTE examination recorded two-dimensional (2D) images, strain by STE, spectral Doppler, colour Doppler, and tissue Doppler imaging (TDI). Images were stored in the standard Digital Imaging and Communications in Medicine (DICOM) format for offline analysis using the proprietary GE post processing software EchoPACS (version 204), which included the Myocardial Work (MW), Automated Function Imaging (AFI) 3.0, AutoEF 3.0, and RV AFI packages. All images were taken with the patient supine to avoid disruption to ongoing clinical management.

Echocardiographic variables

LV end-diastolic internal diameter (LVIDd) was collected from the parasternal long-axis view (PLAX). LV end-diastolic volume and LV end-systolic volume indexed to BSA (LVEDVi and LVESVi respectively) were collected from the apical four-chamber view. LV ejection fraction (LVEF) was calculated using Simpson's biplane method or using the automated EF function in the two- and four-chamber apical views. Global longitudinal strain (GLS %) was measured by using automated tracing of the LV endocardial border in the focused two-, three- and four-chamber apical views (tracings were manually adjusted if needed). Lateral tissue Doppler S' velocity (cm/s) were collected using the four-chamber apical view. For assessment of diastolic function, we collected E/A ratio, E wave deceleration time (ms), left atrial size in end-systole indexed to BSA (LAESVi mL/m^2), and average E/e′ ratio.

We collected the tricuspid regurgitation maximum jet velocity (TR_{regurg} V_{max}), tricuspid annulus plane systolic excursion (TAPSE cm/s), RV S′ velocity (cm/s), RV end-diastolic basal diameter (cm), and RV free wall strain (–%) using the focused RV apical view.

We examined for mitral regurgitation (MR) and mitral stenosis (MS) using the four-chamber apical view, for aortic stenosis (AS) and aortic regurgitation (AR) using the five-chamber apical view, and for tricuspid regurgitation (TR) using the RV focused apical view. Qualitative measurements for regurgitant lesions included vena contracta width (cm) and when possible, determining the proximal isovelocity surface area (PISA) and the effective orifice area (EOA). For stenotic lesions continuous wave Doppler was used to determine maximum transvalvular velocity (m/s). The continuity principle was used to estimate valve areas for stenotic lesions. LV outflow tract diameter (cm) was measured in mid-systole using the PLAX view, LVOT velocity time integral (VTI) was measured using pulsed wave Doppler placed 0.5–1.0 cm within the LVOT in the five-chamber apical view, and heart rate (bpm) were collected to estimate Doppler derived cardiac output (CO L/min), stroke volume (SV ml), and then SV and CO indexed to BSA to give the stroke volume index (SVi ml/m^2) and cardiac index (CI L/min/m^2).

Determination of myocardial work indices

Myocardial work indices were quantified using techniques that have been previously well described[11,28]. Briefly, we measured myocardial strain using three-dimensional speckle tracking echocardiography by tracing the endocardial border seen in the two, three and four chamber LV apical views, and then dividing the LV into a 17-segment model. To create an estimated LV pressure-strain loop the invasive blood pressure and strain data is combined. GE proprietary software then adjusts a normalised reference curve after determining the duration of the different cardiac cycle phases by identifying the opening and closing of the aortic and mitral valve events with manual correction as needed (Fig. 1). By then differentiating the strain data over time per segment this gives the segmental shortening rate. Instantaneous power is then calculated by determining the product of the segmental shortening rate and instantaneous LV pressure. Mathematical integration of this instantaneous power over time finally yields segmental LV myocardial work as a function of time. This provides the following myocardial work indices:

- Global work index (GWI mmHg %) represents the sum of all positive and negative work performed throughout the cardiac cycle (positive work represents normal function of myocardial segments, that is shortening during systole and lengthening during diastole, with negative work representing abnormal function, that is lengthening during systole and shortening during diastole)
- Global constructive work (GCW mmHg %) represents the sum of positive work performed between the mitral valve closing (MVC) and the aortic valve closing (AVC), which includes isovolumetric contraction (IVC) that occurs between MVC and aortic valve opening (AVO), and negative work performed during isovolumetric relaxation (IVR) that occurs between aortic valve closing (AVC) and mitral valve opening (MVO)
- Global wasted work (GWW mmHg %) represents the sum of positive work performed during IVR and negative work performed between MVC and AVC
- Global work efficiency (GWE %) represents the sum of constructive work in all LV segments divided by the sum of both constructive and wasted work in all LV segments

Statistical analysis

Normality of the distribution of continuous variables was assessed using the Shapiro-Wilks test. Continuous data is presented using mean ± standard deviation (SD) or median [interquartile range; IQR]. Censoring was applied to participants who survived until the end of the study period, implying that their survival times were considered as right censored data.

Exact permutation tests were performed to examine the association between measurements recorded on day 1 and day 3 separately, interval changes, and differences in gender on day 1 for MW and RV FWS in relation to 30-day mortality. We used exact permutation tests due to the relatively small sample size of our study, as permutation tests do not rely on parametric assumptions about the distribution of the data. Instead, they calculate p-values by comparing the observed test statistic to the distribution of test statistics generated through resampling. This approach provides an exact and reliable inference and is particularly well-suited for pilot studies with limited sample sizes and when the assumptions of traditional parametric tests, such as normality, cannot be guaranteed. We performed a Bayesian analysis by determining Bayes Factors (BF_{10}) to quantify the strength of evidence for the differences observed. Bayes Factors provide a measure of evidence in favour of the alternate hypothesis (i.e. difference exists) against the null hypothesis (i.e. no difference exists). A noninformative Jeffreys prior was used for the variance of the normal population and a Cauchy prior was used for the standardised effect size. A BF_{10} greater than 1 supports the alternative hypothesis, while a BF_{10} less than 1 favours the null hypothesis. More specifically, a BF_{10} between 1 to 3 indicates anecdotal or weak evidence for the alternative hypothesis, whilst a BF_{10} between 1/3 and 1 indicates anecdotal or weak evidence for the null hypothesis. A BF_{10} equal to 1 suggests no evidence for either hypothesis[29]. Importantly, unlike p-values, Bayes factors allow for continuous evidence evaluation.

We employed a nonparametric percentile bootstrap method to estimate the correlation coefficient (r) and the coefficient of determination (R^2) and their 95% confidence intervals. This involved generating 10,000 resamples of the data by sampling with replacement, calculating the statistic of interest for each resample, and then deriving the confidence intervals from the 2.5th and 97.5th percentiles of the resulting bootstrap distribution. This method was chosen due to its robustness in small sample sizes and its ability to provide reliable interval estimates without assuming normality in the data. For comparing categorical data, Fisher's exact test was used. For variables with < 10% data missing at random, multiple imputation was performed using a predictive mean matching (PMM) method. Intra-observer and inter-observer variability were assessed in 10 randomly selected subjects (4 weeks between repeated assessments) using intraclass correlation coefficients. An alpha level of 0.05 was considered statistically significant. All analyses were performed using R version 4.4.2[30].

Results

From 65 screened patients we recruited 32 patients into the study (56% female; mean age 58.5 ± 14.5 years) (Fig. 2). At 30 days following admission, there were 22 (69%) survivors and 10 (31%) non-survivors. Median survival time for all participants was 458.5 [IQR 23.3–639.3] days. In survivors, the median survival time was 589.0 [IQR 440.3–726.8] days, and in non-survivors 14.5 [IQR 5.3–20.3] days. Baseline characteristics, source of infection and co-morbid conditions in survivors and non-survivors are presented in Table 1. Biochemical, haematological, and baseline echocardiographic and haemodynamic parameters are presented for days 1 and 3 in Table 2. Serum lactate ($p = 0.03$), noradrenaline dose ($p = 0.01$) and SOFA score ($p = 0.00$) on day 3 were significantly different between survivors and non-survivors. In the entire dataset, the number of missing values were as follows for day 1: RV FWS = 3, RV s′ = 1, E/A ratio = 3, E wave deceleration time = 3, E/e′ average = 5. For day 3 they included: RV FWS = 3, RV s′ = 1, E/A ratio = 2, E wave deceleration time = 2, E/e′ average = 9, and highest lactate = 2. As over 50% of day 1 TTE did not have TR amenable to continuous wave Doppler interrogation, this variable was excluded.

Day 1

A marginally significant difference was seen in GWI (1587.2 vs 1165.6 mmHg %; $p = 0.05$, $BF_{10} = 1.53$) and GCW (1805.4 vs 1349.1 mmHg %; $p = 0.05$, $BF_{10} = 1.69$) between survivors and non-survivors. No significant differences were observed in GWW (118.5 vs 131.5 mmHg %; $p = 0.96$, $BF_{10} = 0.40$), GWE (93.0 vs 91.5%; $p = 0.29$, $BF_{10} = 0.42$) or RV FWS (−21.2 vs −19.2%; $p = 0.53$, $BF_{10} = 0.42$) between survivors and non-survivors (Table 3). All four MW variables were found to be quantitatively less in both male and female patients compared to normal values[31] with no significant differences observed (see Supplementary Table S1).

For GLS, GWI ($r = -0.87$, 95% CI (−0.93, −0.76)), GCW ($r = -0.88$, 95% CI (−0.94, −0.77)) and GWE ($r = -0.77$, 95% CI (−0.86, −0.58)) showed strong negative correlations. GWW had a moderately positive correlation ($r = 0.47$, 95% CI (0.13, 0.68)) with GLS (see Supplementary Fig. S1).

For LVEF, both GWI ($r = 0.72$, 95% CI (0.47, 0.86)) and GCW ($r = 0.73$, 95% CI (0.46, 0.88)) had a strong positive correlation. GWW demonstrated a weak negative correlation ($r = -0.34$, 95% CI (−0.58, −0.02)). Lastly, GWE demonstrated a strong positive correlation with LVEF ($r = 0.64$, 95% CI (0.40, 0.76)) (see Supplementary Table S2).

Day 3

GWE demonstrated a significant difference between survivors and non-survivors (94.0 vs 88.5%; $p = 0.02$, $BF_{10} = 1.44$). A marginally significant difference was seen in GWI (1711.5 vs 1270.4 mmHg %; $p = 0.05$, $BF_{10} = 1.53$). There was no significant difference in GCW (1949.2 vs 1559.9 mmHg %; $p = 0.11$, $BF_{10} = 0.95$),

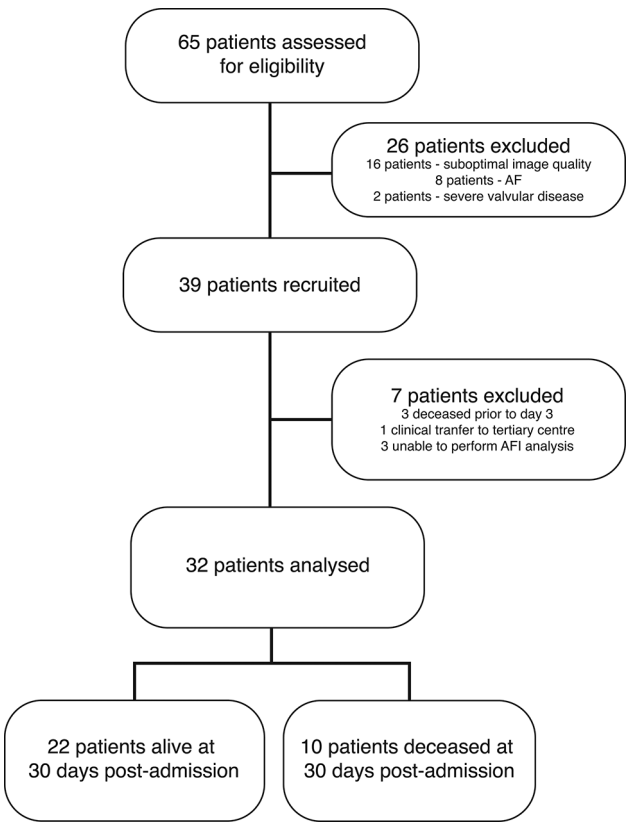

Fig. 2. Patient flow diagram.

Variables	Survivors (n = 22)	Non-survivors (n = 10)	p
Demographics			
Age (years)	55.5 (14.8)	65.2 (11.8)	0.08
BSA (m^2)	1.8 (0.2)	1.9 (0.2)	0.45
BMI	26.6 (6.7)	30.9 (12.0)	0.20
Male:Female	10:12	4:6	1.00
Length of stay (days)	6.0 [3.3–7.0]	10.0 [4.3–17.3]	0.19
Comorbid conditions			
Hypertension	6	5	0.26
CKD	2	1	1.00
Source of infection			
Respiratory	11	8	
Gastrointestinal	4	2	
Genitourinary	3	0	
Musculoskeletal	2	0	
Haematological	1	0	
Central nervous system	1	0	
Valvular abnormalities			
Mild MR	4	2	
Moderate MR	2	3	
Mild AR	0	2	
Moderate AR	1	1	
Mild TR	9	4	
Moderate TR	3	4	
Mild AS	0	1	

Table 1. Patient baseline characteristics; presented as mean (SD) or median [IQR]. *CKD* chronic kidney disease, *MR* mitral regurgitation, *AR* aortic regurgitation, *TR* tricuspid regurgitation, *AS* aortic stenosis. p-values are shown where applicable.

GWW (118.0 vs 161.0 mmHg %; p = 0.16, BF_{10} = 0.68) or RV FWS (−20.5 vs −18.6%; p = 0.47, BF_{10} = 0.45) between survivors and non-survivors (Table 3).

For GLS, GWI (r = −0.91, 95% CI (−0.96, −0.80)), GCW (r = −0.87, 95% CI (−0.95, −0.70)) and GWE (r = −0.79, 95% CI (−0.91, −0.56)) showed strong negative correlations. GWW had a weak positive correlation with GLS (r = 0.31, 95% CI (−0.10, 0.57)) (see Supplementary Fig. S2).

For LVEF, GWI (r = 0.78, 95% CI (0.51, 0.91)) and GCW (r = 0.79, 95% CI (0.56, 0.90)) had strong positive correlations. GWE demonstrated a moderately positive correlation with LVEF (r = 0.57, 95% CI (0.09, 0.79)). GWW showed no relationship with LVEF (r = 0.01, 95% CI (−0.40, 0.37)) (see Supplementary Table S2).

Interval changes between day 1 and day 3

No significant differences in interval changes were seen in GWW (−11.1 vs 52.8 mmHg %; p = 0.08, BF_{10} = 1.19), GWE (2.0 vs −2.2%; p = 0.07, BF_{10} = 1.27), GWI (124.3 vs 104.8 mmHg %; p = 0.90, BF_{10} = 0.36), GCW (143.8 vs 210.8 mmHg %; p = 0.70, BF_{10} = 0.38) or RV FWS (0.8 vs 1.3%; p = 0.82, BF_{10} = 0.38) between survivors and non-survivors (Table 3).

Intraclass correlation coefficients

For GWE, the inter-rater ICC (95% CI) was 0.94 (0.81–0.98). For GWI, the inter-rater ICC (95% CI) were 0.99 (0.97–1.00). For operator 1, using GWE, the intra-rater ICC (95% CI) were 0.97 (0.91–0.99) and for operator 2 were 0.95 (0.74–0.99).

Discussion

In our study, GWE measured on day 3 was significantly associated with 30-day mortality. In addition, between survivors and non-survivors there was found to be a marginally significant difference in GWI and GCW measured on day 1, and GWI measured on day 3. However, the Bayesian analysis provides weak evidence to support these associations, and therefore we consider these results to be tentative. We also did not find a statistically significant difference between survivors and non-survivors in the interval changes in MW and RV FWS. However, Bayesian analysis also suggests weak evidence in favour of a difference, but our evidence is not strong enough to draw definitive conclusions. MW was reduced in both male and female patients on admission compared to normal values and there was no significant difference observed between sexes. Both GLS and LVEF showed strong correlations with GWI, GCW, and GWE. However, GWW had a much weaker correlation with both GLS and LVEF.

Variable	Survivors (n = 22)	Non-survivors (n = 10)	p
Day 1			
Hb (g/L)	100.8 (19.5)	88.4 (22.2)	0.12
WCC ($\times 10^9$/L)	13.6 [8.0–17.9]	13.1 [10.0–21.9]	0.71
Platelets ($\times 10^9$/L)	190.5 [91.8–285.3]	152.0 [106–267.3]	0.92
Urea (mmol/L)	10.1 [9.2–20.7]	12.7 [10.8–15.5]	0.76
Creatinine (mmol/L)	126.0 [93.8–213.8]	148.5 [111–192.3]	0.65
Bilirubin (mmol/L)	13 [6.7–23.7]	15 [6.3–28.0]	0.66
Lactate (mmol/L)	2.1 [1.4–2.8]	3.1 [1.6–5.4]	0.24
SOFA score	7 [5–9]	8 [6–9]	0.66
Noradrenaline (mcg/kg/min)	0.1 [0.0–0.2]	0.1 [0.1–0.2]	0.98
GLS (%)	− 16.7 (4.6)	− 13.8 (6.5)	0.16
LVEF (%)	55.0 (10.1)	52.2 (20.5)	0.62
LVIDd (cm)	4.5 [4.2–5.0]	4.7 [4.4–4.9]	0.37
LVEDVi (mL/m^2)	42.4 [33.6–48.0]	43.2 [34.6–61.3]	0.67
LVESVi (mL/m^2)	17.5 [15.7–20.0]	22.4 [12.4–36.8]	0.53
LAESVi (mL/m^2)	32.5 (14.1)	32.3 (10.2)	0.97
E/a ratio	1.1 [0.9–1.4]	1.3 [1.1–1.5]	0.22
E wave decel time (ms)	180.0 [159.0–218.0]	184.0 [152.0–224.0]	0.83
E/e′ average	7.3 [6.1–8.3]	10.4 [7.0–15.4]	0.12
RV basal diameter (cm)	4.6 (0.7)	4.1 (0.6)	0.21
TAPSE (cm)	2.1 (0.8)	1.9 (0.6)	0.25
RV s′ (cm/s)	14.1 [11.0–19.0]	13.0 [12.0–16.5]	0.58
CO (L/min)	5.9 [4.4–6.8]	4.64 [2.7–6.8]	0.35
CI (L/min/m^2)	3.3 [2.4–3.6]	2.5 [1.7–3.3]	0.13
SV (mL)	69.5 [56.5–80.5]	52 [34.2–85.5]	0.37
SVi (mL/m^2)	36.6 [30.3–47.9]	30.1 [19.9–43.3]	0.13
SBP (mmHg)	116 [105–125]	103 [92–112]	0.07
DBP (mmHg)	61 [58–67]	55 [46–68]	0.22
HR (beats/minute)	84 (22)	83 (13)	0.95
Day 3			
Hb (g/L)	91.0 [90.0–117.5]	87.0 [82.3–89.0]	0.22
WCC ($\times 10^9$/L)	12.5 [9.7–15.5]	16.4 [8.3–19.3]	0.47
Platelets ($\times 10^9$/L)	168.5 [118.5–295.8]	152.0 [118.3–270.0]	0.62
Urea (mmol/L)	9.4 [7.1–18.2]	15.4 [12.1–19.4]	0.12
Creatinine (mmol/L)	104.0 [74.8–180.0]	158.0 [74.5–206.0]	0.53
Bilirubin (mmol/L)	8.0 [5.7–12.8]	14.5 [9.5–26.8]	0.21
Lactate (mmol/L)	1.1 [0.9–1.4]	1.7 [1.6–2.0]	**0.03**
SOFA score	4 [2–5]	8 [6–9]	**0.00**
Noradrenaline (mcg/kg/min)	0.0 [0.0–0.0]	0.1 [0.0–0.2]	**0.01**
GLS (%)	− 17.3 (4.4)	− 13.6 (7.2)	0.09
LVEF (%)	57.3 (10.6)	50.3 (18.1)	0.18
LVIDd (cm)	4.8 [4.4–5.1]	4.7 [4.6–4.9]	0.93
LVEDVi (mL/m^2)	48.1 [34.2–58.8]	48.6 [33.6–62.6]	0.91
LVESVi (mL/m^2)	19.2 [15.3–22.4]	24.3 [13.1–34.6]	0.32
LAESVi (mL/m^2)	31.2 [22.5–38.1]	32.8 [22.4–40.2]	0.85
E/a ratio	1.2 [1.1–1.5]	1.2 [1.0–1.3]	0.44
E wave decel time (ms)	198.0 [171.0–241.0]	254.0 [150.0–271.0]	0.65
E/e′ average	7.9 [6.3–10.2]	10.0 [8.1–10.7]	0.27
RV basal diameter (cm)	3.9 [3.5–4.1]	3.6 [3.4–4.2]	0.67
TAPSE (cm)	2.2 (0.5)	1.9 (0.6)	0.10
RV s′ (cm/s)	15.0 [13.2–18.0]	14.5 [11.1–16.5]	0.44
CO (L/min)	5.2 [4.5–6.0]	5.1 [2.7–6.0]	0.44
CI (L/min/m^2)	2.8 [2.5–3.4]	2.5 [1.5–3.0]	0.12
SV (mL)	73.0 [54.6–84.4]	55.5 [35.0–80.5]	0.27
SVi (mL/m^2)	38.3 [29.9–52.8]	29.0 [19.0–36.1]	0.06
SBP (mmHg)	117 [112–140]	113 [107–119]	0.29
Continued			

Variable	Survivors (n = 22)	Non-survivors (n = 10)	p
DBP (mmHg)	62 [55–77]	58 [51–65]	0.27
HR (beats/minute)	75 (15)	85 (13)	0.09

Table 2. Biochemical and echocardiographic parameters according to 30-day mortality separated into day 1 and day 3; presented as mean (SD) or median [IQR]. *SOFA* sequential organ failure assessment, *LVEF* left ventricle ejection fraction, *LVIDd* left ventricle internal diameter in diastole, *LVEDVi* left ventricle end diastolic volume index, *LVESVi* left ventricle end systolic volume index, *TAPSE* tricuspid annulus plane systolic excursion, *CO* cardiac output, *CI* cardiac index, *SV* stroke volume, *SVi* stroke volume index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate. Significant values are in bold.

Variable	Survivors (n = 22)	Non-survivors (n = 10)	p	Bayes factor
Day 1				
GWI (mmHg %)	1587.2 (488.2)	1165.6 (671.5)	0.05	1.53
GCW (mmHg %)	1805.4 (525.0)	1349.1 (685.4)	0.05	1.69
GWW (mmHg %)	118.5 [87.8 to 172]	131.5 [70.3 to 157.5]	0.96	0.40
GWE (%)	93.0 [89.0 to 95.0]	91.5 [81.3 to 93.8]	0.29	0.42
RV FWS (%)	− 21.2 (12.0)	− 19.2 (14.1)	0.53	0.42
Day 3				
GWI (mmHg %)	1711.5 (472.3)	1270.4 (762.7)	0.05	1.53
GCW (mmHg %)	1949.2 (523.3)	1559.9 (811.0)	0.11	0.95
GWW (mmHg %)	118.0 [57.3 to 191.8]	161.0 [102.8 to 235.8]	0.16	0.68
GWE (%)	94.0 [91.0 to 96.0]	88.5 [84.8 to 92.3]	**0.02**	1.44
RV FWS (%)	− 20.5 (7.8)	− 18.6 (11.0)	0.47	0.45
Interval changes				
GWI (mmHg %)	124.3 (355.3)	104.8 (522.4)	0.90	0.36
GCW (mmHg %)	143.8 (397.8)	210.8 (543.0)	0.70	0.38
GWW (mmHg %)	− 11.1 (81.7)	52.8 (112.0)	0.08	1.19
GWE (%)	2.0 (5.1)	− 2.2 (7.5)	0.07	1.27
RV FWS (%)	0.8 [− 1.7 to 5.4]	1.3 [− 3.5 to 4.0]	0.82	0.38

Table 3. Myocardial work and RV FWS parameters for survivors (n = 22) and non-survivors (n = 10) at 30 days according to day 1 and day 3—presented as mean (standard deviation) or median [interquartile range]. Interval changes are shown with positive and negative numbers representing an increase or decrease in the variable between day 1 and day 3. Significant values are in bold.

We believe that this is the first study to apply MW in critical care patients presenting with sepsis. Comparing our findings to that of the European Association of Cardiovascular Imaging (EACVI) Normal Reference Ranges for Echocardiography (NORRE) study, we observe that both male and female patients with sepsis had lower than normal values for myocardial work indices (see Supplementary Table S1)[31]. However, it is important to note that the mean age of the cohort studied in the EACVI NORRE study was less than the mean age in our study. Furthermore, we demonstrated that GWE in non-survivors was comparable to GWE observed in post-infarct patients, but not as significantly reduced as that observed in patients with heart failure[28]. Finally, some of our findings can be compared with Orde et al.'s study on STE parameters in sepsis mortality prediction[24]. Both studies found no significant differences in traditional echocardiographic markers or LV GLS between survivors and non-survivors. Orde et al. identified significant differences in RV FWS at 6 months suggesting this as a predictor of mortality. However, this difference was not present at 30 days. Our study, limited to RV FWS measurements on day 1 and day 3, did not observe a significant difference in RV FWS. This may suggest that RV dysfunction, undetectable acutely, could emerge later, potentially after cardiac remodelling.

We speculated that in sepsis, myocardial work is reduced, and this is evidenced by our findings on day 1 and day 3. By comparing measurements recorded on day 1 and day 3, we observe that the GCW and GWW increased and decreased in survivors by approximately 8% and 0.4% respectively. In non-survivors, the GCW and GWW increased by approximately 16% and 22% respectively. So, despite observing a relatively greater increase in GCW in non-survivors, the even greater increase in GWW appears to be the most important factor in the decrease in GWE in non-survivors. A mechanistic explanation of our results is inherently fraught with challenges, as sepsis induced myocardial dysfunction may have both protective and deleterious pathways which both result in myocardial depression. The relatively low values of GWI and GCW across all patients compared to normal expected values may be the result of protective myocardial depression. This is likely to be multifactorial in aetiology but may involve beta-adrenergic receptor downregulation[32] and uncoupling of associated G-protein messaging which reduces calcium influx and myocyte contractility[33]. Explaining the increase in GWW is

more difficult. It is not inherently obvious that protective, hibernating processes would increase GWW as by definition this work 'wastes' energy without contributing to cardiac output. Impaired myocardial energetics may partially explain the increased GWW seen. Mitochondrial dysfunction, secondary to oxidative stress and free radical accumulation, is common in sepsis and causes mitochondrial structural damage and reduces adenosine triphosphate (ATP) output[34]. Whilst theoretically reduced ATP output leading to myocardial suppression may reduce oxygen demand and be protective, mitochondrial damage is also likely to lead to irreversible cellular damage. Inextricably linked to mitochondrial dysfunction is understanding how changes in metabolomics may affect myocardial energetics.

Under normal conditions the heart relies on fatty acid oxidation (FAO) for most of its ATP production. In the setting of sepsis FAO rates can fall and whilst glucose metabolism via glycolysis may increase it cannot compensate entirely, leaving the cardiac myocyte in an energy deficit. Additionally, this suppression of FAO leads to lipid accumulation inside the myocyte, impairing contractility[8] as demonstrated by the relative increase in GWW observed in non-survivors. It has long been understood that gross coronary perfusion is not impaired in sepsis, and that coronary blood flow increases[35]. However, abnormalities in microcirculation may also be a contributing factor in the increased GWW seen. Microvascular dysfunction secondary to endothelial dysfunction, heterogeneity in capillary flow, excess nitric oxide induced vasodilation and leukocyte adhesions can lead to microcirculatory dysfunction and local malperfusion[34]. Whilst this may not lead to frank regional ischaemia, it may contribute to occult demand ischaemia[36], which in turn give rise to impaired regional contractility of cardiac muscle that can be detected using MW.

It is plausible that a combination of the mechanistic explanations above would explain our finding of increased GWW and reduced GWE in sepsis. An ultimate mismatch in supply and demand of energy in the form of ATP to the myocyte could result from a combination of microvascular dysfunction, suppression of fatty acid oxidation and mitochondrial dysfunction. This coupled with histological changes of lipid and inflammatory product accumulation[34], and possible demand-related micro-ischaemia poses a conceivable multifactorial explanation for our findings.

Despite providing valuable insights into myocardial function using echocardiography in patients presenting with sepsis, there are several limitations to our study. The comparisons made in MW and RV FWS are limited by the small study sample size and therefore it has insufficient power to detect smaller differences and limited our ability to perform robust multivariable analyses to adjust for potential confounders. Furthermore, as a single centre study with a limited number of patients, the generalisability of our findings to other critical care populations and different healthcare settings remains uncertain. Additionally, in critical care patients, suboptimal acoustic windows can pose a challenge to echocardiographic assessments, potentially affecting the feasibility and accuracy of myocardial work measurements. We recognise that by performing TTE only on days 1 and 3 of admission, we have not fully captured the dynamic changes in cardiac function that could occur beyond this period. Thus, some important variations in myocardial function may not be accounted for. In addition, our mortality outcome was limited to 30 days and, therefore, the study did not assess the long-term effects of MW and RV FWS. To further enhance our understanding of MW in patients with sepsis, we believe that larger cohort studies are both feasible and necessary to confirm the observed difference in GWE between survivors and non-survivors. Longitudinal studies capturing serial echocardiographic data could offer deeper insights into the progression of sepsis related cardiac dysfunction with respect to MW and RV FWS. Future research should explore the interplay between sepsis-induced mitochondrial dysfunction, fatty acid oxidation suppression, and microcirculatory impairment in relation to myocardial energetics. Incorporating advanced metabolomics and imaging techniques such as MW and RV FWS could elucidate the underlying metabolic shifts contributing to energy deficits in the myocardium. Also, expanding the outcomes to include long-term mortality and morbidity beyond 30 days could clarify the chronic impacts of myocardial dysfunction in sepsis survivors. Given the relatively small number of patients in this pilot study, we chose not to perform sensitivity analyses, as the limited sample size might have rendered such analyses less reliable or inconclusive. Future studies with larger cohorts should incorporate sensitivity analyses to confirm the stability of findings. Lastly, as this was a pilot observational study, echocardiographic findings did not directly influence patient management. The study was designed to assess the feasibility and potential clinical relevance of myocardial work analysis rather than to guide treatment decisions. While our findings suggest potential associations with patient outcomes, further interventional studies are required to determine whether myocardial work-guided management strategies can improve clinical outcomes in sepsis.

Conclusion

This study aimed to explore whether myocardial work (MW) and right ventricular free wall strain (RV FWS) are linked to 30-day mortality in sepsis patients. It found that survivors had higher global work efficiency (GWE) compared to non-survivors on day 3 of admission, suggesting reduced efficiency in non-survivors was largely due to increased global wasted work (GWW). No significant interval changes in MW or RV FWS were detected. In addition, on admission, both male and female patients had lower MW and RV FWS values compared to normal and no significant differences were observed between sexes. The relevance of this study lies in its novel use of MW in critical care and proposes GWW as a potential therapeutic target for improving outcomes in patients presenting with sepsis. This study serves as a reminder to clinicians that ventricular performance in the context of sepsis is complex: an efficient ventricle which performs minimal wasted work seems to be most associated with survival at 30 days. However, MW indices cannot be evaluated using traditional echocardiographic techniques and so high levels of vigilance remain necessary even following a normal echocardiographic report lacking MW assessment in critical care patients presenting with sepsis.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions
Thomas Sanderson [TS1] contributed to the development of the research methodology, conducted patient recruitment, performed echocardiography examinations, created Fig. 1 outlining myocardial work and contributed to the writing of the manuscript. Theophilus Samuels [TS2] contributed to the conceptualisation of the study, development of the research methodology, performed the data and statistical analysis, conducted patient recruitment, performed echocardiography examinations, digitalised the concept of Fig. 1 for publication, created Fig. 2 and contributed to the writing of the manuscript. All authors read and approved the final manuscript.

Declarations

Competing interests
The authors declare no competing interests.

Ethical approval and consent to participate
The study was approved by the London Bromley Research Ethics Committee (ref 21/LO/0303). Informed consent was either obtained from patients prior to participating, or where the patient was incapacitated, informed consent was obtained from their next of kin.

Additional information
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