Research Square

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Biventricular dysfunction, pre-existing cardiac disease, and mortality in sepsis: an echocardiographic cohort study

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Abstract

Background.

Sepsis frequently affects both ventricles, yet whether right ventricular (RV) and combined biventricular dysfunction carry prognostic weight independent of illness severity—and how much reflects acute injury rather than pre-existing cardiac disease—remains uncertain. We characterised biventricular phenotypes and their association with mortality in a large sepsis cohort.

Methods.

In a retrospective single-centre cohort from the MIMIC-IV and MIMIC-IV-ECHO databases, we studied 8,209 adults with sepsis (Sepsis-3) who underwent a resting transthoracic echocardiogram within 72 hours of ICU admission that reported both left ventricular (LV) ejection fraction and RV systolic function. Patients were classified as having normal biventricular function or isolated LV, isolated RV, or biventricular dysfunction. Associations with 28-day, 90-day, and in-hospital mortality were estimated by logistic and Cox regression and by modified Poisson regression (adjusted risk ratios), adjusting for illness severity, comorbidity, and pre-existing cardiac disease. Additive interaction (relative excess risk due to interaction, RERI), dose-response, and prespecified sensitivity and subgroup analyses were performed.

Results.

Normal biventricular function was present in 4,747 patients (57.8%), isolated LV dysfunction in 1,171 (14.3%), isolated RV dysfunction in 850 (10.4%), and biventricular dysfunction in 1,441 (17.6%). Twenty-eight-day mortality rose across phenotypes (22.9%, 26.4%, 31.3%, and 34.8%). After adjustment, all three phenotypes remained independently associated with 28-day mortality (odds ratio 1.27, 1.35, and 1.50, respectively), with biventricular dysfunction carrying the highest risk; the joint LV–RV effect did not depart significantly from additivity (RERI − 0.08, 95% CI − 0.27 to 0.10). Higher RV dysfunction grade and pulmonary artery systolic pressure were associated with higher mortality. The associations were attenuated when pre-existing cardiac disease was unaccounted for and were concentrated among patients without pre-existing cardiac disease, among whom the isolated-RV association was attenuated to the null. Findings were consistent across sensitivity and subgroup analyses.

Conclusions.

In sepsis, biventricular dysfunction identifies the highest-risk echocardiographic phenotype, with the excess risk concentrated among patients without pre-existing cardiac disease, a pattern consistent with acute, de novo ventricular involvement.

Introduction

Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1], is among the leading causes of death in the intensive care unit (ICU) and accounts for nearly one in five deaths worldwide [2]. Cardiovascular failure is central to its pathophysiology, and restoration of tissue perfusion is a cornerstone of management [3].

Cardiac involvement in sepsis—commonly termed sepsis-induced cardiomyopathy—has traditionally been viewed through a left ventricular (LV) lens, dating to the classic description of profound but reversible depression of LV systolic function in septic shock [4, 5]. Although contemporary echocardiographic studies confirm that LV systolic and diastolic abnormalities are common [6], their prognostic significance has been inconsistent: a reduced LV ejection fraction (LVEF) has repeatedly failed to predict mortality [7], whereas diastolic dysfunction has shown a more reproducible association with death [8]. The load dependence of LVEF and heterogeneous diagnostic definitions have contributed to this uncertainty [4].

The right ventricle (RV) has received considerably less attention. RV dysfunction is increasingly recognized in sepsis, where it may result from direct myocardial depression and from increased afterload related to pulmonary vascular dysfunction and positive-pressure ventilation [4]. Available studies suggest it carries prognostic weight: isolated RV dysfunction was independently associated with worse long-term survival in a single-center cohort [9], and a meta-analysis of 1,373 patients linked RV dysfunction to higher short- and long-term mortality [10]. This evidence, however, derives largely from small single-center studies with heterogeneous definitions, and quantitative RV indices such as tricuspid annular plane systolic excursion are frequently unobtainable at the bedside [11].

Importantly, LV and RV dysfunction often coexist, yet the two ventricles are usually examined in isolation. Whether RV dysfunction conveys prognostic information beyond LV dysfunction and shared illness severity, whether the ventricles act independently or interact, and how combined (biventricular) involvement compares with isolated dysfunction remain poorly defined—largely because adequately powered cohorts with structured, paired LV and RV assessment have been lacking.

The recent incorporation of structured echocardiographic measurements into a large, publicly available critical-care database now enables such an analysis at scale. We used this resource to define biventricular phenotypes in a large sepsis cohort and to examine (i) the independent association of isolated LV, isolated RV, and biventricular dysfunction with mortality; (ii) whether the joint effect of LV and RV dysfunction departs from additivity; and (iii) the dose-response relationships of RV dysfunction severity and pulmonary pressures with outcome.

Methods

Study design and data source

We performed a retrospective cohort study using the Medical Information Mart for Intensive Care IV (MIMIC-IV) database [12] and its echocardiographic module, MIMIC-IV-ECHO [13], both hosted on PhysioNet [14]. MIMIC-IV (version 3.1) contains de-identified electronic health-record data for patients admitted to the ICUs of the Beth Israel Deaconess Medical Center; MIMIC-IV-ECHO (version 1.0) additionally provides structured echocardiographic report measurements linked to these admissions through the stable patient identifier. The study is reported in accordance with the STROBE statement [15]. Because the database is de-identified and publicly accessible, a waiver of informed consent applies. Full details of the data source, cohort definition, echocardiographic measurement processing, covariate definitions, and statistical methods are provided in Additional file 1: Supplementary Methods.

Study population

We included adults (≥ 18 years) who met the Sepsis-3 criteria [1] during their first ICU admission and who underwent a resting transthoracic echocardiogram (TTE) within 72 hours of ICU admission reporting both an interpretable RV functional assessment and a left ventricular ejection fraction (LVEF). Only the first qualifying study per patient was analysed. We excluded studies in which RV function could not be evaluated (e.g., “RV not well seen,” “cannot assess”) and those with a hyperdynamic or otherwise unclassifiable RV, as well as records with non-evaluable LVEF.

Echocardiographic exposures and biventricular phenotypes

LVEF and RV function were obtained from the structured measurements. When LVEF was reported as a range, a single value was taken as the midpoint when the upper bound was below 100% and the range width was ≤ 15 percentage points, and as the lower bound otherwise; this convention, and the inherent imprecision of interval-reported LVEF, are acknowledged as a potential source of non-differential misclassification. LV systolic dysfunction was defined as LVEF < 50%, in line with cardiac chamber-quantification recommendations [16]. RV function was classified from the reporting cardiologist's categorical assessment, interpreted according to American Society of Echocardiography right-heart guidelines [11], into normal versus dysfunctional and—for dose-response analysis—into an ordinal severity grade (none, mild, moderate, severe; Additional file 1: Table S2). Patients were assigned to four mutually exclusive phenotypes: normal biventricular function, isolated LV dysfunction, isolated RV dysfunction, and biventricular (combined) dysfunction. Where available, the reported pulmonary artery systolic pressure (PASP), estimated by the interpreting cardiologist from the tricuspid regurgitation jet, and the peak tricuspid regurgitation velocity were recorded; the availability of quantitative echocardiographic measurements is summarized in Additional file 1: Table S1.

Covariates

Pre-specified covariates were age, sex, illness severity (Sequential Organ Failure Assessment [SOFA] score at sepsis onset [17]), comorbidity burden (Charlson comorbidity index [18]), atrial fibrillation, the

maximum serum lactate within 24 hours of admission (natural-log transformed, median-imputed where missing), any vasopressor use within 24 hours summarised as the norepinephrine-equivalent dose [19], maximum acute kidney injury stage within 48 hours defined and entered as an ordinal variable per the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [20], and pre-existing cardiac disease (a composite of heart failure, coronary artery disease, valvular disease, and cardiomyopathy ascertained from discharge diagnoses).

Outcomes

The primary outcome was 28-day all-cause mortality, with time zero set at the echocardiogram. Secondary outcomes were 90-day mortality (time-to-event) and in-hospital mortality.

Statistical analysis

Baseline characteristics were summarised by phenotype. The association of each phenotype with 28-day and in-hospital mortality was estimated by logistic regression (odds ratios [ORs]), and with 90-day mortality by Cox proportional-hazards regression (hazard ratios [HRs]); the proportional-hazards assumption was assessed with Schoenfeld residuals. Models were fitted both unadjusted and adjusted for the pre-specified covariates, with the normal-function group as reference. Because the outcome was common—a setting in which ORs overstate risk ratios—we additionally estimated adjusted risk ratios using modified Poisson regression with robust variance [21]. Departure from additivity of the LV and RV effects was quantified by the relative excess risk due to interaction (RERI) with its 95% confidence interval, and multiplicative interaction was tested by a likelihood-ratio test of the LV-by-RV product term [22]. Dose-response was examined using the ordinal RV severity grade and PASP, the latter modelled both in quartiles and as a continuous variable using restricted cubic splines. Survival across phenotypes was compared with Kaplan–Meier curves and the log-rank test. Pre-specified sensitivity analyses comprised: an alternative LV threshold (LVEF < 40%); exclusion of patients with pre-existing cardiac disease; a model omitting the pre-existing-cardiac-disease covariate; a complete-case analysis restricted to patients with measured lactate; additional adjustment for invasive mechanical ventilation within 24 hours; the continuous norepinephrine-equivalent dose; and, for dose-response, exclusion of an ambiguously labelled RV category. Eleven patients with missing 90-day follow-up time were excluded from the time-to-event analysis only. Analyses were performed in R (version 4.5.2; R Foundation for Statistical Computing, Vienna, Austria); two-sided $P < 0.05$ defined statistical significance.

Results

Cohort characteristics

Among septic adults admitted to the ICU with a qualifying early resting transthoracic echocardiogram, 8,209 patients met all eligibility criteria and formed the analytic cohort (Fig. 1). Normal biventricular function was present in 4,747 patients (57.8%), isolated LV dysfunction in 1,171 (14.3%), isolated RV

dysfunction in 850 (10.4%), and biventricular dysfunction in 1,441 (17.6%). Patients with any ventricular dysfunction, and those with biventricular dysfunction in particular, were older, more frequently male, carried a higher comorbidity burden, and presented with greater acute illness severity, reflected by higher SOFA scores and lactate concentrations and more frequent vasopressor use and acute kidney injury (Table 1). Pre-existing cardiac disease was far more common in the three dysfunction groups than in the reference group (73.4–92.9% versus 50.1%). Median LVEF remained 60% in the two groups with preserved LV function and fell to 38% and 30% in the isolated-LV and biventricular groups, respectively, whereas PASP was highest among patients with isolated RV dysfunction (median 40 mmHg).

Table 1
Baseline characteristics of the analytic cohort, overall and by biventricular phenotype.

Characteristic	Normal both	Isolated LV	Isolated RV	Biventricular	Overall	P
No. of patients	4747	1171	850	1441	8209	
Age, years	68 [56–80]	72 [61–81]	71 [60–81]	70 [60–79]	69 [58–80]	< 0.001
Male sex	2364 (49.8)	724 (61.8)	447 (52.6)	959 (66.6)	4494 (54.7)	< 0.001
SOFA score	3 [2–4]	3 [2–4]	3 [2–5]	4 [2–5]	3 [2–5]	< 0.001
Charlson index	5 [3–7]	7 [5–8]	6 [4–8]	7 [5–9]	6 [4–8]	< 0.001
Atrial fibrillation	1505 (31.7)	437 (37.3)	412 (48.5)	720 (50.0)	3074 (37.4)	< 0.001
Lactate, mmol/L	1.9 [1.3–3.3]	2.0 [1.4–3.3]	2.0 [1.4–3.9]	2.7 [1.7–4.7]	2.1 [1.4–3.6]	< 0.001
Vasopressor ≤ 24 h	2007 (42.3)	525 (44.8)	446 (52.5)	877 (60.9)	3855 (47.0)	< 0.001
AKI, KDIGO ≥ 1	3435 (72.4)	884 (75.5)	699 (82.2)	1210 (84.0)	6228 (75.9)	< 0.001
Prior cardiac disease	2376 (50.1)	1058 (90.4)	624 (73.4)	1338 (92.9)	5396 (65.7)	< 0.001
Invasive ventilation ≤ 24 h	2234 (47.1)	602 (51.4)	451 (53.1)	795 (55.2)	4082 (49.7)	< 0.001
LVEF, %	60 [55–68]	38 [30–42]	60 [55–65]	30 [22–38]	55 [42–65]	< 0.001
PASP, mmHg	31 [25–38]	32 [25–40]	40 [30–52]	34 [26–42]	32 [25–41]	< 0.001
28-day mortality	1087 (22.9)	309 (26.4)	266 (31.3)	501 (34.8)	2163 (26.3)	< 0.001
90-day mortality	1422 (30.0)	402 (34.3)	342 (40.2)	653 (45.3)	2819 (34.3)	< 0.001
In-hospital mortality	909 (19.1)	254 (21.7)	229 (26.9)	437 (30.3)	1829 (22.3)	< 0.001

Data are median [IQR] or n (%). P values are from the Kruskal–Wallis test (continuous) or χ^2 test (categorical) comparing the four phenotypes. Lactate was available in 76.0% and PASP in 73.3% of patients; summary statistics for these variables are based on non-missing observations. AKI, acute kidney injury; IQR,

interquartile range; KDIGO, Kidney Disease: Improving Global Outcomes; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; SOFA, Sequential Organ Failure Assessment.

Biventricular phenotype and mortality

Crude mortality increased monotonically across the four phenotypes, from 22.9% in patients with normal biventricular function to 26.4%, 31.3%, and 34.8% in the isolated-LV, isolated-RV, and biventricular groups for the 28-day outcome, with parallel gradients at 90 days (30.0%, 34.3%, 40.2%, and 45.3%) and in hospital (19.1%, 21.7%, 26.9%, and 30.3%) (Table 1; all $P < 0.001$). Kaplan–Meier curves separated early and diverged progressively (log-rank $P < 0.001$; Fig. 2).

In unadjusted logistic models, the odds of 28-day death relative to normal biventricular function were increased for isolated LV dysfunction (OR 1.21, 95% CI 1.04–1.40), isolated RV dysfunction (OR 1.53, 1.31–1.80), and biventricular dysfunction (OR 1.79, 1.58–2.04) (Table 2). After adjustment for illness severity, comorbidity, and cardiovascular substrate, all three phenotypes remained independently associated with 28-day mortality: isolated LV dysfunction OR 1.27 (1.08–1.49), isolated RV dysfunction OR 1.35 (1.13–1.60), and biventricular dysfunction OR 1.50 (1.29–1.74) (Fig. 3). Adjustment attenuated the isolated-RV and biventricular associations relative to their crude estimates, whereas the isolated-LV association was marginally strengthened; the convergence of the isolated-LV and isolated-RV estimates indicates that the substantially larger crude effect of RV dysfunction was largely explained by its co-occurrence with greater illness severity. The 90-day Cox models reproduced this pattern (adjusted HR 1.21, 1.28, and 1.48 for isolated-LV, isolated-RV, and biventricular dysfunction, respectively; Table 2), and the proportional-hazards assumption was satisfied for all three phenotype terms. Estimates were materially similar when expressed as adjusted risk ratios from modified Poisson regression (isolated LV 1.18, 1.06–1.32; isolated RV 1.20, 1.08–1.34; biventricular 1.30, 1.18–1.43), confirming that the odds ratios modestly overstated the relative risks for this common outcome.

Table 2
Unadjusted and adjusted associations of biventricular phenotype with mortality.

Phenotype	Deaths/total	Unadj. OR (95% CI)	Adj. OR (95% CI)	Unadj. HR (95% CI)	Adj. HR (95% CI)
Normal biventricular	1087/4747	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]
Isolated LV	309/1171	1.21 (1.04–1.40)	1.27 (1.08–1.49)	1.18 (1.06–1.32)	1.21 (1.07–1.36)
Isolated RV	266/850	1.53 (1.31–1.80)	1.35 (1.13–1.60)	1.46 (1.29–1.64)	1.28 (1.13–1.44)
Biventricular	501/1441	1.79 (1.58–2.04)	1.50 (1.29–1.74)	1.71 (1.56–1.88)	1.48 (1.33–1.64)

Odds ratios are from logistic regression for 28-day all-cause mortality; hazard ratios are from Cox proportional-hazards regression for 90-day all-cause mortality. Deaths/total are shown for the 28-day

outcome. Adjusted models include age, sex, SOFA score, Charlson comorbidity index, atrial fibrillation, natural-log lactate, vasopressor use within 24 hours, KDIGO AKI stage, and pre-existing cardiac disease. Corresponding adjusted risk ratios (modified Poisson) were 1.18, 1.20, and 1.30 for isolated-LV, isolated-RV, and biventricular dysfunction. The identical rounded values of the unadjusted 90-day hazard ratio and the adjusted risk ratio for isolated LV dysfunction (both 1.18) are coincidental; to three decimals they are 1.184 and 1.181, respectively. CI, confidence interval; HR, hazard ratio; LV, left ventricular; OR, odds ratio; RV, right ventricular.

Absence of interaction between LV and RV dysfunction

The joint effect of LV and RV dysfunction was consistent with independent, additive contributions rather than synergy. On the multiplicative scale, the LV×RV interaction term was not significant (adjusted interaction OR 0.88, 95% CI 0.68–1.13; likelihood-ratio P = 0.30; unadjusted P = 0.79). On the additive scale, the relative excess risk due to interaction, calculated from the adjusted risk ratios, was − 0.08 (95% CI − 0.27 to 0.10), indicating no meaningful supra-additive effect, although the confidence interval does not exclude a modest departure from additivity.

Pulmonary pressures and RV-grade dose–response

Among the 6,013 patients with an estimable PASP, higher pressures were associated with higher 28-day mortality in a graded fashion (22.2%, 24.0%, 26.6%, and 33.0% across ascending quartiles), corresponding to an adjusted OR of 1.15 per 10 mmHg (95% CI 1.09–1.20); the relationship was confirmed on restricted-cubic-spline modelling (Additional file 1: Fig. S1). The severity of qualitative RV dysfunction likewise showed a dose–response relationship with mortality (adjusted OR per grade 1.13, 95% CI 1.07–1.19); in a sensitivity analysis excluding an ambiguously labelled RV category, the gradient became strictly monotonic and the adjusted trend strengthened to 1.20 (1.12–1.28). The full distributions are provided in Additional file 1: Tables S3 and S4.

Sensitivity analyses

The principal findings were robust across prespecified sensitivity analyses (Additional file 1: Table S5). Replacing the binary vasopressor indicator with the maximum norepinephrine-equivalent dose, adding invasive mechanical ventilation as a covariate, using in-hospital death as the outcome, restricting the analysis to patients with measured lactate, and redefining LV dysfunction at an LVEF threshold of < 40% each yielded essentially unchanged estimates (e.g., with mechanical-ventilation adjustment: isolated LV 1.23, isolated RV 1.33, biventricular 1.49). Pre-existing cardiac disease behaved as a negative confounder: in a model omitting this covariate, the isolated-LV association was abolished (OR 1.04) and the biventricular association fell to 1.20, whereas the fully adjusted model preserved the prognostic signal of acute, de novo dysfunction. Consistent with this interpretation, when the analysis was restricted to the 2,813 patients without pre-existing cardiac disease—in whom ventricular dysfunction is most likely to be acute—the associations for isolated LV and biventricular dysfunction strengthened (OR 1.66, 1.08–2.55 and 2.21, 1.42–3.43), whereas the estimate for isolated RV dysfunction was attenuated

to the null (OR 1.03, 0.74–1.43). A direct stratification of mortality by phenotype and pre-existing cardiac disease was concordant: among patients with isolated LV or biventricular dysfunction, 28-day mortality was markedly higher in the absence of pre-existing cardiac disease, whereas isolated-RV mortality in this de novo group approximated that of patients with normal biventricular function (Additional file 1: Table S7).

Subgroup and robustness analyses

Graphical summaries of the sensitivity and subgroup analyses for the biventricular phenotype are shown in Fig. 4. The association was preserved across all prespecified sensitivity analyses (Fig. 4A), including the model omitting pre-existing cardiac disease, the complete-case analysis, additional adjustment for invasive mechanical ventilation, the norepinephrine-equivalent dose, the in-hospital outcome, and the alternative LVEF threshold. Across prespecified clinical subgroups (Fig. 4B and Additional file 1: Table S6), the adjusted odds ratio for biventricular dysfunction was essentially unchanged by age (1.50 in patients < 65 years; 1.49 in those ≥ 65 years) and sex (1.52 in men; 1.53 in women), and remained significant among patients with and without septic shock (1.79 and 1.30), with and without invasive mechanical ventilation (1.50 and 1.43), and in those with acute kidney injury (1.55); the confidence interval crossed unity only in the small subgroup without acute kidney injury (1.25, 0.83–1.89). Tests for interaction were non-significant for sex, septic shock, mechanical ventilation, and acute kidney injury (all $P > 0.10$); a nominal age interaction ($P = 0.03$) was attributable to the isolated phenotypes, the biventricular estimate being identical across age strata. These subgroup analyses were prespecified but exploratory and were not adjusted for multiple comparisons.

Discussion

In this large cohort of patients with sepsis and paired left- and right-ventricular assessment, isolated LV, isolated RV, and biventricular dysfunction were each independently associated with higher short- and long-term mortality, with biventricular dysfunction carrying the greatest risk. The effects of LV and RV dysfunction combined approximately additively, with no evidence of multiplicative or additive synergy, and mortality rose in a graded fashion with both RV dysfunction severity and pulmonary artery systolic pressure. The prognostic signal appeared concentrated in acute, de novo dysfunction: the associations were attenuated—and for isolated LV no longer significant—when pre-existing cardiac disease was left unaccounted for, and were stronger when the analysis was restricted to patients without pre-existing cardiac disease, among whom the isolated-RV association was attenuated to the null, although the smaller numbers in this subgroup limit precision.

These observations are best understood through the distinction between acute, sepsis-induced ventricular dysfunction and chronic, compensated dysfunction. Sepsis-induced cardiomyopathy is classically an acute and potentially reversible depression of myocardial function [4, 5], whereas patients with chronic cardiac disease enter sepsis with longstanding, compensated impairment. Pre-existing cardiac disease was common in our dysfunction groups and behaved as a negative confounder: it is strongly associated with the presence of ventricular dysfunction, yet—conditional on dysfunction—with

comparatively lower acute mortality, so that adjusting for it unmasked the lethality of acute, de novo dysfunction. This interpretation is consistent with prior work showing that pre-existing LV systolic dysfunction does not worsen sepsis mortality [23], and that LV dysfunction detected during sepsis—often a mixture of acute and chronic disease—has shown inconsistent prognostic value [24]. Indeed, even when sepsis-induced cardiomyopathy is defined strictly as a new-onset reduction in LVEF, its reported impact on mortality remains inconsistent [25]. The same lens resolves the apparent paradox in our isolated-RV results, where the independent association disappeared once the cohort was restricted to acute dysfunction.

Framed in this way, our findings help reconcile a longstanding inconsistency in the literature. Meta-analyses have repeatedly found that a low LVEF does not predict mortality in sepsis [7], whereas indices more reflective of acute decompensation, such as diastolic dysfunction, are more consistently associated with death [8]. Because LVEF is load-dependent and conflates chronic with acute impairment, an unadjusted analysis dilutes the acute signal—mirroring the nullification of our isolated-LV association when pre-existing disease was ignored. The high prevalence of myocardial dysfunction in sepsis [6] therefore reflects a heterogeneous mixture whose prognostic meaning depends on chronicity rather than on the mere presence of dysfunction.

Our RV findings extend, and partly qualify, previous reports. Isolated RV dysfunction has been associated with worse survival in single-center cohorts [9] and in meta-analysis [10], and RV dilatation accompanies troponin release and adverse outcome in severe sepsis [26]. In our data, isolated RV dysfunction was independently associated with mortality overall, but this association was attenuated to the null among the smaller subset of patients with acute, de novo dysfunction, suggesting that much of its apparent prognostic value reflects coexisting chronic cardiopulmonary disease and the severity of the precipitating insult rather than an independently lethal acute lesion. This accords with the pathophysiology of acute RV dysfunction in critical illness, which is tightly coupled to afterload—pulmonary vascular dysfunction, hypoxaemia, hypercapnia, and positive-pressure ventilation—as exemplified by acute cor pulmonale in ARDS, where RV failure is driven by infectious lung injury and high driving pressures and is associated with mortality [27, 28]. By contrast, the consistent and substantial risk associated with biventricular dysfunction, persisting even in the de novo subset, identifies combined acute ventricular involvement as the genuinely high-risk phenotype.

Clinically, these findings argue for distinguishing acute from chronic ventricular dysfunction rather than treating every reduced LVEF or abnormal RV as equivalent. Because acute sepsis-induced myocardial depression is frequently reversible, some early ventricular dysfunction or dilatation may accompany survivable illness rather than portend death [29]. Acute, de novo biventricular dysfunction instead identifies the highest-risk patients and may warrant closer hemodynamic surveillance and right-ventricle–aware management—judicious fluid administration, afterload reduction, and lung-protective ventilation to limit RV strain [27]. Translating these signals to the bedside, however, remains constrained by the persistent absence of a unified definition of septic cardiomyopathy [4, 30] and by the

heterogeneity of cardiac involvement across the syndrome [31]. Moreover, a preserved LVEF can mask impaired contractility detectable only by speckle-tracking strain [32].

Our study complements earlier database analyses. At the same institution, but in the predecessor MIMIC-III database, the performance of transthoracic echocardiography itself was associated with lower 28-day mortality in sepsis [33], yet that work did not identify which echocardiographic findings carry prognostic weight. By structuring paired LV and RV measurements in more than eight thousand patients, prespecifying covariates, and reporting odds ratios alongside risk ratios together with a formal additive-interaction analysis and multiple sensitivity analyses, we move from whether echocardiography helps toward which phenotype matters. The direction of our biventricular findings is concordant with meta-analyses linking sepsis-induced cardiomyopathy to higher mortality [34], even as the reported prevalence of such dysfunction varies widely with the definition applied [35]. The large sample also enabled dose-response analyses across RV severity and pulmonary pressures—and resolution of the prognosis of isolated RV dysfunction—that smaller single-center cohorts could not support [36].

This study has limitations. First, it is retrospective and single-center, and echocardiography was performed at clinician discretion, so the cohort is enriched for patients in whom cardiac assessment was deemed necessary; because patients had to survive long enough to undergo echocardiography, the most rapidly fatal early deaths are under-represented, which may bias the associations toward the null and limit generalisability; the associations are not causal. Second, RV function was derived from categorical clinical reports rather than quantitative indices such as tricuspid annular plane systolic excursion or strain, which were too sparsely recorded to analyse; although this reflects routine documentation, the complex, afterload-dependent physiology of the septic right ventricle may not be fully captured by a qualitative label [37]. Third, LVEF was frequently reported as an interval, introducing non-differential misclassification, and global LV systolic function in sepsis is itself dynamic and load-dependent, varying with vasopressor support [38]. Fourth, pre-existing cardiac disease was ascertained from discharge diagnoses and the acute-versus-chronic distinction was inferred rather than measured against a baseline echocardiogram; discharge codes cannot temporally separate pre-existing from incident cardiac disease, and the suppressor pattern may in part reflect more intensive cardiac treatment, or less complete diagnostic coding of brief fatal admissions, in patients with recognised cardiac disease, so residual confounding cannot be excluded—although the concordance of the suppressor analysis, the de novo subset, and the dose-response relationships supports the interpretation. Because acute cases miscoded as pre-existing disease would dilute the acute-versus-chronic contrast, any such misclassification would, if anything, render the observed pattern conservative. Finally, serum lactate was incompletely recorded, although estimates were unchanged in complete-case analysis, and in-hospital mortality was modelled by logistic regression without accounting for the competing risk of discharge.

In conclusion, in a large cohort of patients with sepsis, isolated LV, isolated RV, and biventricular dysfunction were each independently associated with mortality, with biventricular dysfunction carrying the greatest, approximately additive risk. The prognostic signal was concentrated in acute, de novo

dysfunction: once chronicity was accounted for, isolated RV dysfunction was no longer independently lethal, whereas acute biventricular involvement remained the highest-risk phenotype. These findings reframe ventricular dysfunction in sepsis around acuity rather than the mere presence of abnormality, and identify acute biventricular dysfunction as a high-risk prognostic phenotype whose incremental value for risk stratification warrants prospective evaluation.

Abbreviations

AKI
acute kidney injury
ARDS
acute respiratory distress syndrome
CI
confidence interval
HR
hazard ratio
ICU
intensive care unit
IQR
interquartile range
KDIGO
Kidney Disease:Improving Global Outcomes
LV
left ventricular
LVEF
left ventricular ejection fraction
MIMIC-IV
Medical Information Mart for Intensive Care IV
OR
odds ratio
PASP
pulmonary artery systolic pressure
RERI
relative excess risk due to interaction
RV
right ventricular
SOFA
Sequential Organ Failure Assessment
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology

TAPSE
tricuspid annular plane systolic excursion
TTE
transthoracic echocardiogram.

Declarations

Ethics approval and consent to participate.

This study used the de-identified MIMIC-IV database and its MIMIC-IV-ECHO module. The establishment of MIMIC-IV was approved by the institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center, which granted a waiver of informed consent for the collection and analysis of these de-identified data. Access was obtained through the PhysioNet credentialing process and completion of the required data use agreement; the corresponding author completed the mandated human-subjects research training (CITI “Data or Specimens Only Research”). Because the data are publicly available and de-identified, no additional institutional review board approval was required for the present secondary analysis. The study was conducted in accordance with the Declaration of Helsinki and is reported in line with the STROBE guidance for observational studies.

Consent for publication.

Not applicable.

Clinical trial number.

Not applicable.

Competing interests.

The authors declare that they have no competing interests.

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Author Contribution

HT conceived and designed the study. LS extracted the data, performed the statistical analysis, and drafted the manuscript. GL and YY contributed to data interpretation and critically revised the

manuscript for important intellectual content. HT supervised the study and revised the manuscript. All authors read and approved the final manuscript.

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Data Availability

The data that support the findings of this study are available from PhysioNet (https://physionet.org) to credentialed users who have completed the required training and signed the data use agreement: MIMIC-IV (https://physionet.org/content/mimiciv/3.1/) and MIMIC-IV-ECHO (https://physionet.org/content/mimic-iv-echo/1.0/). The analytic code and the exact cohort-extraction queries used in this study are openly available in the Zenodo repository (https://doi.org/10.5281/zenodo.20641095).

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Figures

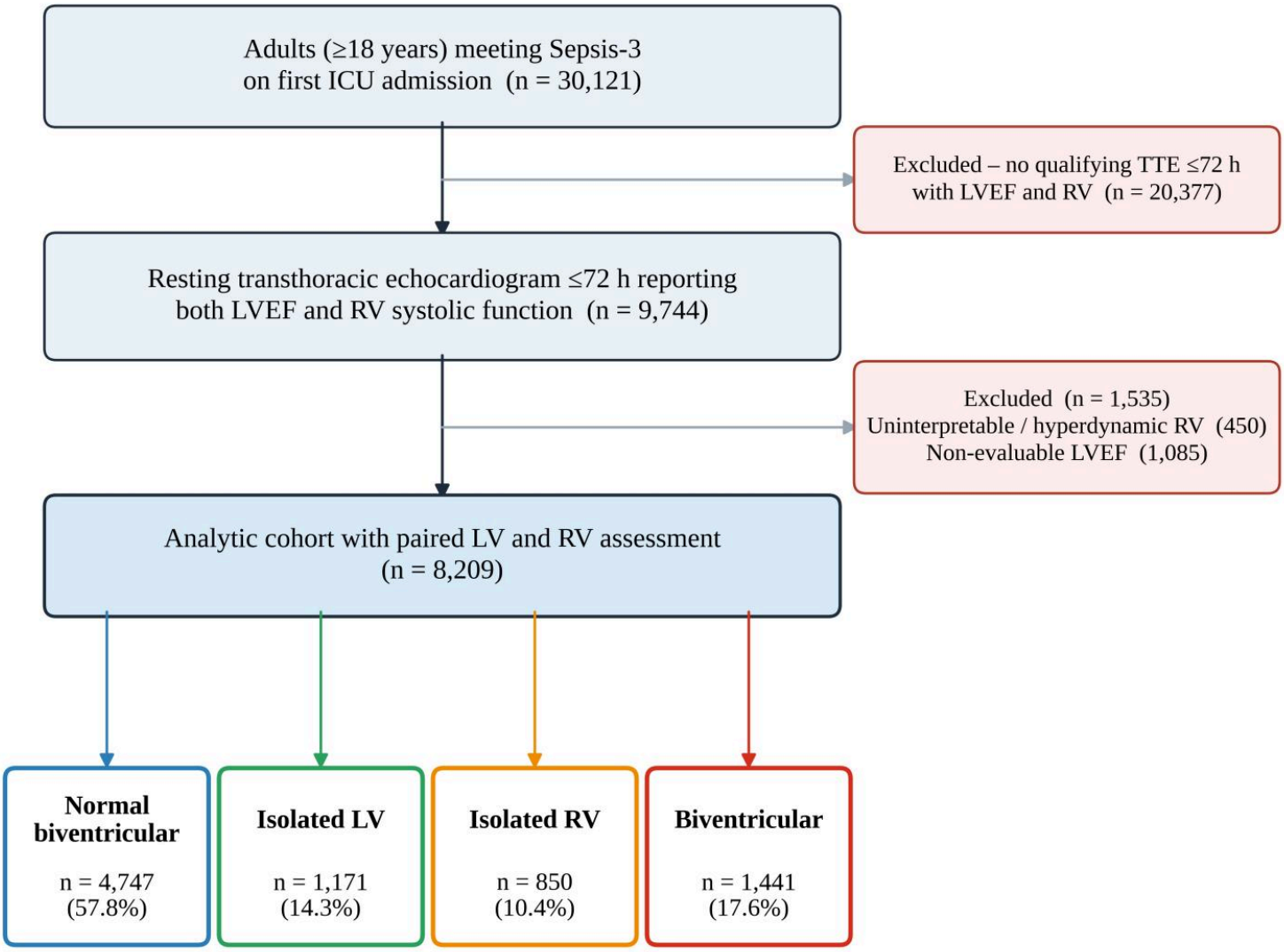
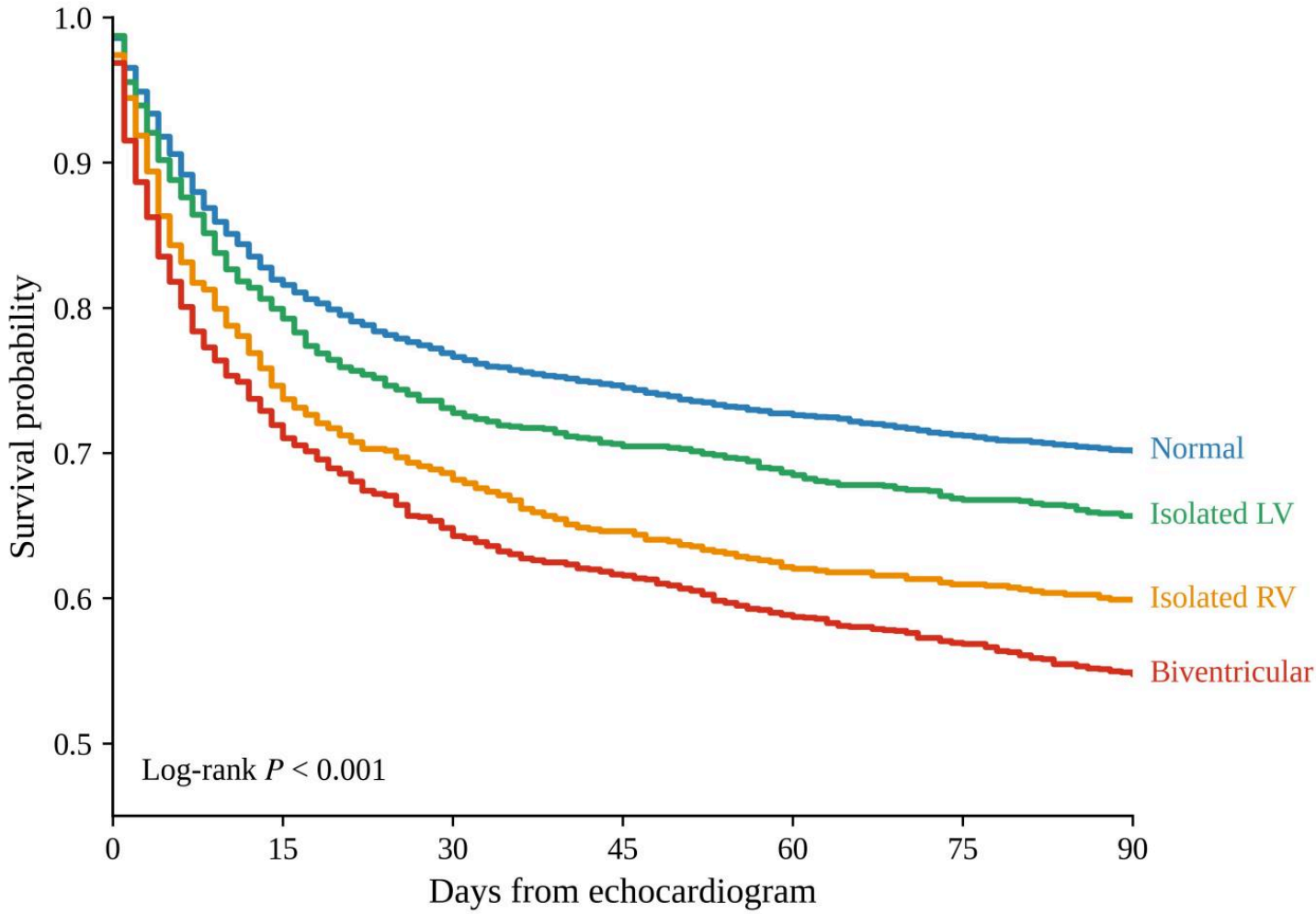


Figure 1

Cohort assembly. Of 30,121 adults with sepsis (Sepsis-3) and a first ICU admission, 20,377 were excluded because they did not have a resting transthoracic echocardiogram within 72 hours that reported both LVEF and RV systolic function. Of the 9,744 patients with a qualifying study, 450 were excluded for an uninterpretable or hyperdynamic RV reading and 1,085 for a non-evaluable LVEF value or an RV reading that could not be classified, leaving 8,209 patients in the analytic cohort. ICU, intensive care unit; LVEF, left ventricular ejection fraction; RV, right ventricular; TTE, transthoracic echocardiogram.



Number at risk

Normal	4740	3884	3644	3539	3448	3377	3327
Isol. LV	1171	936	856	827	804	783	769
Isol. RV	848	633	582	548	527	517	508
Biventr.	1439	1035	933	887	847	819	790

Figure 2

Ninety-day survival by biventricular phenotype. Kaplan–Meier survival estimates from the time of the index echocardiogram for the four mutually exclusive phenotypes. The between-group comparison is by the log-rank test (P<0.001; n=8,198 patients with available follow-up time); the numbers of patients at risk are shown below the time axis. LV, left ventricular; RV, right ventricular.

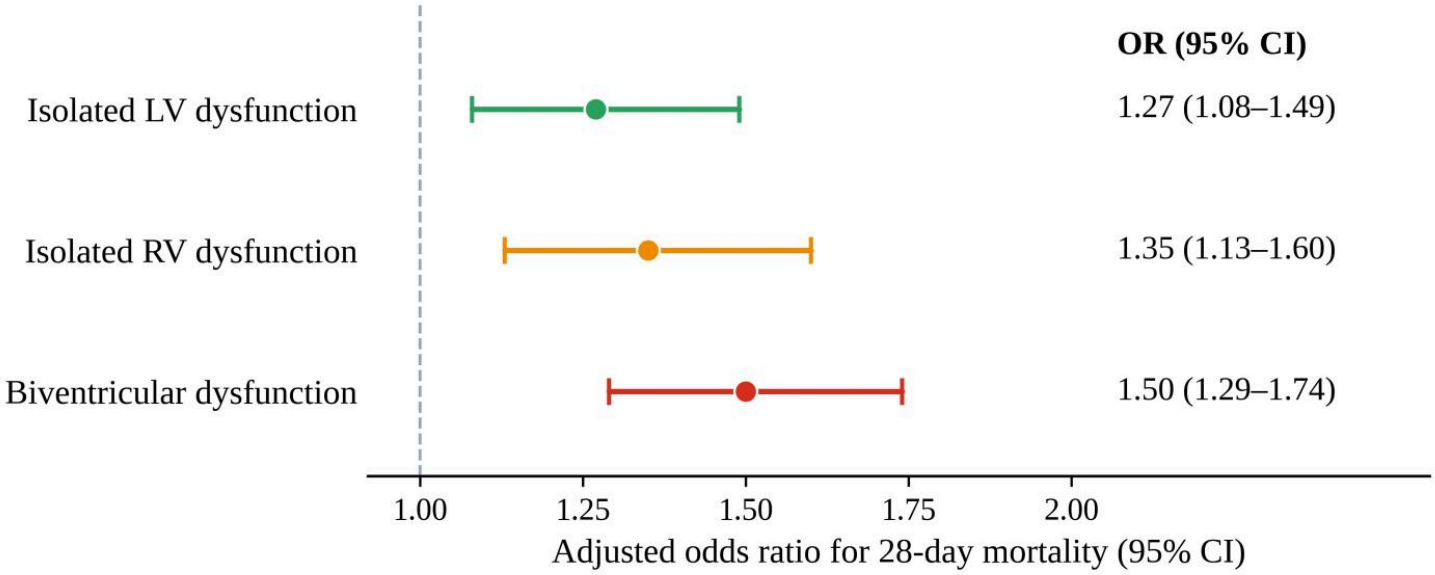


Figure 3

Adjusted associations of biventricular phenotype with 28-day mortality. Forest plot of adjusted odds ratios (logistic regression) relative to normal biventricular function, with 95% confidence intervals. All models are adjusted for the prespecified covariate set (see Methods and the footnote to Table 2). The vertical reference line denotes the null value. CI, confidence interval; LV, left ventricular; OR, odds ratio; RV, right ventricular.

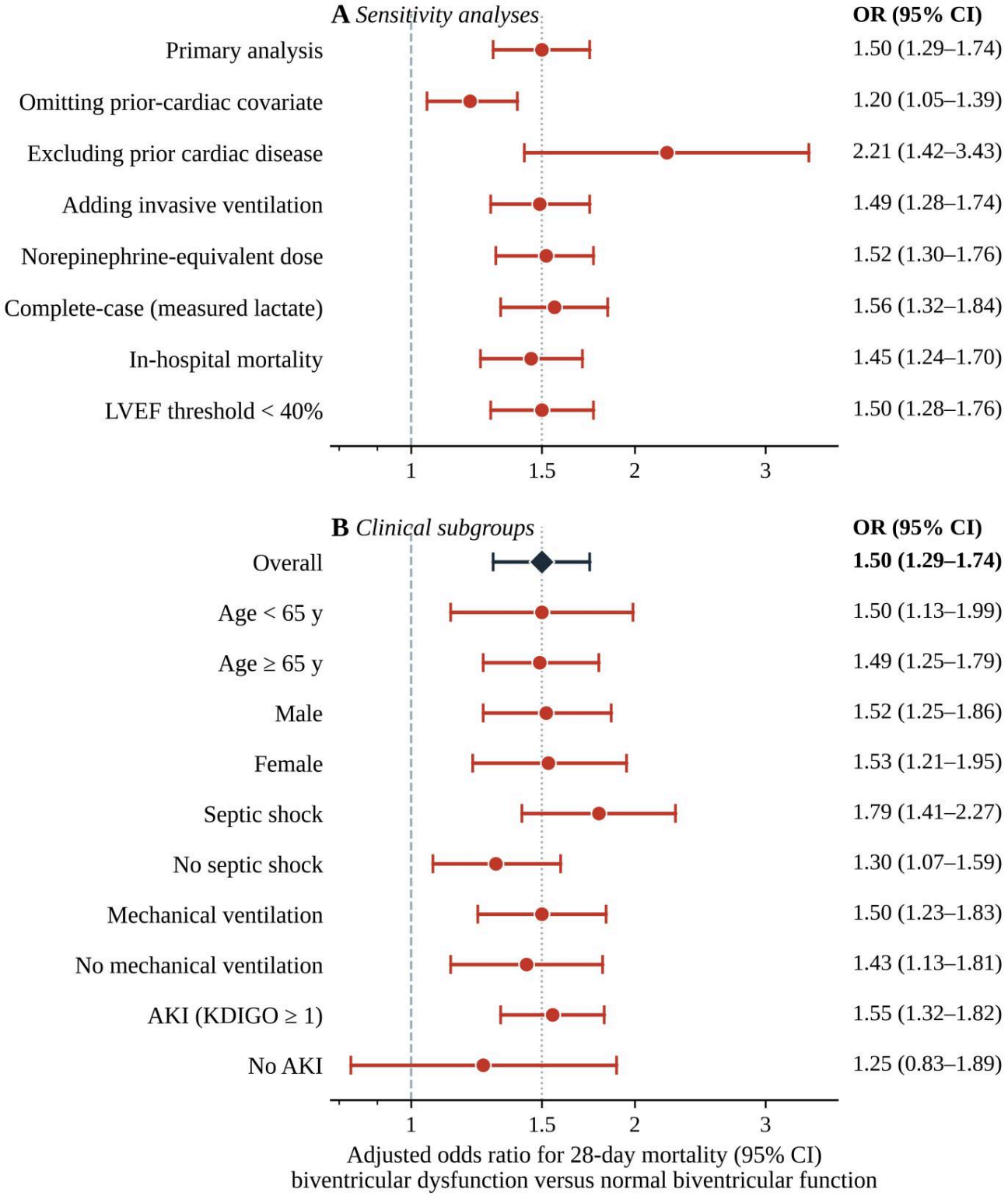


Figure 4

Robustness of the association between biventricular dysfunction and 28-day mortality. Adjusted odds ratios for biventricular dysfunction versus normal biventricular function are shown for (A) prespecified sensitivity analyses and (B) prespecified clinical subgroups; the overall estimate is marked by a diamond in panel B. Horizontal bars denote 95% confidence intervals, the dashed line marks the null value, and the dotted line marks the overall estimate. All models are adjusted for the prespecified covariate set, except that the

variable defining a subgroup was omitted within that subgroup. AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes; LVEF, left ventricular ejection fraction; OR, odds ratio.

Supplementary Files

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