Heliyon 10 (2024) e33599

Contents lists available at ScienceDirect

Heliyon

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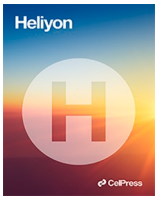

Research article

Association between early central venous pressure measurement and all-cause mortality in critically ill patients with heart failure: A cohort of 11,241 patients

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ARTICLE INFO

Keywords:
Central venous pressure$_1$
Early measurement$_2$
Heart failure$_3$
Critical care$_4$
All-cause mortality$_5$
MIMIC-IV database$_6$

ABSTRACT

Background: The timing of central venous pressure (CVP) measurement may play a crucial role in heart failure management, yet no studies have explored this aspect.
Methods: Clinical information pertaining to patients in critical condition with a diagnosis of heart failure was retrieved from the MIMIC-IV database. The association between initial measurements of central venous pressure (CVP) and the incidence of mortality from all causes was analyzed using the Cox proportional hazards approach. Subgroup analysis and propensity score matching were conducted for sensitivity analyses.
Results: This study included 11,241 participants (median age, 75 years; 44.70 % female). Utilizing restricted cubic spline and Kaplan–Meier survival analyses, it was determined that prognostic outcomes were better when CVP was measured within the initial 5-h window. Multivariate-adjusted 1-year (HR: 0.69; 95 % CI: 0.61–0.77), 90-day (HR: 0.70; 95 % CI: 0.62–0.80), and 30-day (HR: 0.67; 95 % CI: 0.57–0.78) all-cause mortalities were significantly lower in patients with early CVP measurement, which was proved robustly in subgroup analysis. Subsequent to the application of propensity score matching, a cohort of 1536 matched pairs was established, with the observed mortality rates continuing to be significantly lower among participants who underwent early CVP assessment.
Conclusions: Early CVP measurement (within 5 h) demonstrated an independent correlation with a decrease in both immediate and extended all-cause mortality rates among patients in critical condition suffering from heart failure.

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https://doi.org/10.1016/j.heliyon.2024.e33599
Received 30 December 2022; Received in revised form 13 June 2024; Accepted 24 June 2024
Available online 25 June 2024

1. Introduction

Heart failure, a clinical syndrome marked by elevated intracardiac pressures and/or reduced cardiac output, represents a critical stage of any cardiac injury, whether due to structural or functional anomalies [1,2]. Individuals facing life-threatening health states, especially those receiving treatment in the intensive care unit (ICU), often experience profound cardiac insufficiency and cardiogenic shock, which results in diminished life expectancy and a decline in the quality of their living conditions [1]. According to data from the Mayo Clinic, 12.5 % of ICU patients with heart failure faced in-hospital death, and 52.8 % of survivors were readmitted or died within 1 year of discharge [3]. Recognizing prognostic indicators in patients with heart failure who are critically ill is crucial, as these factors can inform subsequent therapeutic strategies and enhance patient clinical results [4–6].

There is a closely associated relationship between venous congestion and the inadequate perfusion of peripheral tissues, which significantly correlates with adverse outcomes in patients suffering from heart failure who are in a critical state [7,8]; hence, hemodynamic assessment is considered critical. In opposition to the established knowledge regarding the pathophysiology of heart failure, evidence from prior clinical studies indicates that the incorporation of extra hemodynamic surveillance in heart failure patients did not result in superior outcomes when contrasted with sole clinical evaluation [9,10]. Thus, guidelines did not recommend the routine use of hemodynamics in patients with heart failure [1,2]. Nevertheless, we believe that the clinical value of hemodynamic evaluation is underestimated. The above conclusions were restricted by factors such as imperfect design and patient selection, and the researchers did not consider the timing of the hemodynamic intervention.

Central venous pressure (CVP), a representative hemodynamic metric, can reflect a patient's volume status and intracardiac filling pressure. The measurement of CVP was associated with the prognostic outcomes in individuals suffering from heart failure [11–13]. A small-sample prospective study indicated that elevated CVP levels in decompensated heart failure patients in the emergency room independently forecasted the likelihood of cardiac rehospitalization [11]. Another study found that an extreme CVP-extracellular volume status ratio (too high or low) tended to match more cardiac events in patients with acute heart failure [12]. Individuals presenting with acute heart failure who exhibited lower CVP values tended to have a higher incidence of short-term renal function deterioration [13].

Considering that central venous pressure (CVP) is a frequently utilized metric in ICU patients [14], it's surprising that there's a scarcity of comprehensive studies investigating the correlation between CVP and clinical outcomes in critically ill heart failure patients. The moment of CVP intervention plays a crucial role in the subsequent treatment of these patients. Yet, the association between when CVP intervention occurs and the outcomes for patients with critical heart failure has not been thoroughly investigated. This study, which looks back at a substantial number of cases, aims to illuminate how early assessments of CVP impact the overall death rates in patients suffering from severe heart failure, thus underlining once more the critical role of hemodynamic monitoring in guiding therapy for these individuals.

2. Materials and methods

2.1. Data sources

This investigation constitutes a single-institution retrospective cohort study, utilizing the Multiparameter Intelligent Monitoring in Intensive Care IV (MIMIC-IV, version 2.0) database to compile all heart failure patient records. The MIMIC-IV database, a joint creation by the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center (BIDMC), offers free global access to researchers. It includes all patient admissions to BIDMC's ICU from 2008 through 2019. In addition to sourcing patients' death dates from the hospital's system, MIMIC-IV also verifies these details against state records, employing identifiers like names, birth dates, and social security numbers. Follow-up for each patient extended up to one year following their ultimate hospital discharge.

2.2. Statement of ethics and authorization

The establishment and oversight of the MIMIC-IV database were sanctioned by the ethics committees at the Massachusetts Institute of Technology and BIDMC. All identifying information of the clinical subjects was removed, and the requirement for informed consent was waived by BIDMC. The investigators, when solicited, passed the "Protecting Human Research Participants" test and obtained permission to use the MIMIC-IV database (Record ID: 43449634). This study's reporting protocols adhere to the STROBE guidelines.

2.3. Study population

In the MIMIC-IV database, all heart failure patients were subjected to initial screening, and only the inaugural ICU admission was considered for those with multiple entries. Heart failure identification relied on the ICD-9 and ICD-10 codes. These codes are detailed in the Supplementary Table S1. Exclusion criteria included patients under 18 years of age or those with an ICU duration shorter than 24 h. Additionally, organ donors were omitted due to their negative survival time calculations. The primary analysis encompassed 11,241 subjects, with 1913 receiving CVP assessments within the initial 5 h, and the remainder experiencing postponed or absent CVP evaluations.

2.4. Research variable and outcomes

The focus of the study was the early assessment of CVP, defined as a CVP reading obtained within the initial 5 h post-ICU admission. The main endpoint was the incidence of all-cause mortality after one year. Secondary endpoints included all-cause mortality at intervals of 30 and 90 days, the length of stay in the ICU, the volume of intravenous fluids administered during the first three days of ICU stay, and the number of days not requiring mechanical ventilation or vasopressors in the first 30 days following ICU admission.

2.5. Data Extraction and preparation

Employing PostgreSQL software (version 9.6, available at the official portal: https://www.postgresql.org/), data was retrieved for all participants in the study from the MIMIC-IV database. This dataset comprised demographic information such as age, gender, and race; severity indices like the Sequential Organ Failure Assessment (SOFA) and Simplified Acute Physiology Score II (SAPSII) at ICU entry; physical exam findings including mean arterial pressure (MAP), cardiac rhythm, breathing rate, body temperature, peripheral oxygen saturation, and body mass; laboratory evaluations covering complete blood count, anion gap, electrolyte levels, and clotting factors; comorbid conditions such as hypertension, diabetes, atrial fibrillation, acute heart attack, heart valve disease, heart muscle disease, and additional comorbidities ascertained by the ICD-9 and ICD-10; the computed Charlson comorbidity score; therapeutic interventions like artificial ventilation, circulatory support, renal replacement therapy, vasopressors, and diuretic therapy on the day of ICU admission; and nursing data including administered IV fluids and urine output on day one. Importantly, the initial timing and value of CVP measurements were also collected. Missing data for these variables are presented in Supplemental Table S2. Variables with over a 20 % absence of data were omitted from further analysis, and those with lesser missing data underwent multiple imputation procedures.

2.6. Statistical analysis

For variables that are continuous, we denote them using the mean ± standard deviation when they conform to normal distribution and have equal variances. If not, we express them as the median (interquartile range). We describe categorical variables by the number of occurrences (percentage). In comparing continuous variables, we utilize either the Student's t-test or the Mann–Whitney *U* test. For categorical variables, we apply the chi-square test or Fisher's exact test.

The analysis utilized a restricted cubic spline within the framework of the Cox proportional hazards model to delineate the nonlinear relationship between the initial CVP measurement timing or value and the all-cause mortality risk. Survival differences among patients who underwent early CVP measurement versus those who did not were depicted through Kaplan–Meier survival curves. Hypothesis testing was conducted with the log-rank test.

To shed more light on the connection between initial CVP measurements and principal outcomes, we conducted both univariate and multivariate Cox regression analyses. The findings are reported as hazard ratios (HRs) with their corresponding 95 % confidence intervals (CIs). The basic model did not adjust for any variables. Model I was adjusted for demographic factors including age, sex, and ethnicity. Model II expanded on Model I by adjusting for additional variables such as disease severity scores (SOFA and SAPS II), physiological signs (weight, heart rate, respiratory rate, and mean arterial pressure [MAP]), results from laboratory tests (anion gap, chloride, and blood urea nitrogen), presence of malignancy, Charlson comorbidity index, and first-day treatments (mechanical ventilation, dialysis, and vasopressors), as well as the type of ICU. Covariate selection was based on two criteria: 1. The factor's influence on the research variable must be greater than 10 %. 2. Factors that are known from previous experience to significantly affect outcomes. The variance inflation factor was employed to assess multicollinearity among the variables, leading to the exclusion of prothrombin time and hematocrit due to their high collinearity.

To validate the strength of our results, Propensity Score Matching (PSM) and Inverse Probability of Treatment Weighting (IPTW) were applied, using propensity scores to adjust for confounding variables. The propensity scores for patients receiving early CVP measurements were derived using multivariate logistic regression. A 1:1 nearest neighbor matching algorithm with a caliper width of 0.25 was implemented for PSM. IPTW calculations employed the predicted probabilities from the logistic model to generate robust inverse probability weights. The Standardized Mean Difference was used to evaluate the balance achieved by PSM and IPTW. Post-PSM, survival patterns were depicted using Kaplan–Meier curves, and the matched groups were analyzed using Cox regression.

The subgroup analysis aimed to determine the consistency of the association between early CVP measurement and one-year all-cause mortality across various subgroups. These subgroups were defined by characteristics including age, gender, ethnicity, disease severity, initial CVP values, and types of heart failure. The findings from this analysis bolstered the credibility of our conclusions.

To dissect the overall impact of an intervention, causal mediation analysis was utilized to differentiate between the direct and indirect influences, with the latter being channeled through a distinct mediator. The analytical summary included the mean causal mediation influence, mean direct influence, and cumulative effects. In our research, we identified the initial measurement of CVP as the intervention and chose pivotal elements (serum anion gap, CVP, and MAP) as the intermediaries to explore if the initial CVP measurement's impact on the main outcome was conveyed through these significant elements.

Statistical evaluations were conducted employing R software (version 4.2.2) and EmpowerStats software (version 3.0; X&Y Solutions, Inc., Boston, MA, USA) on the Windows platform. We established the criterion for statistical significance at a *P*-value less than 0.05 (two-tailed).

3. Results

3.1. Baseline characteristics

As depicted in Fig. 1, 11,241 critically ill patients with heart failure were included in this study. The cohort had a median age of 75

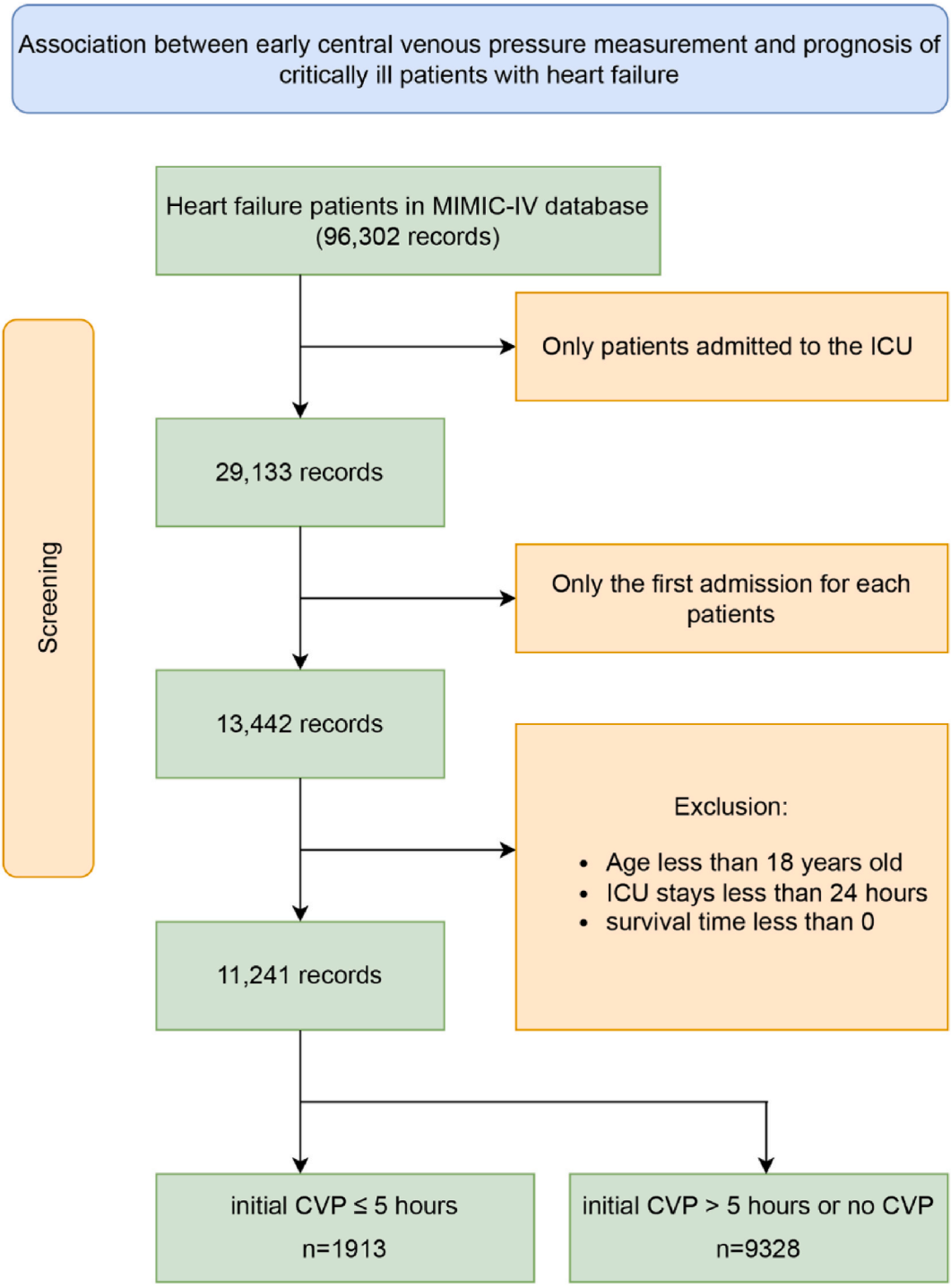

Fig. 1. Flow diagram for selecting patients from the MIMIC-IV database. MIMIC-IV, Multiparameter Intelligent Monitoring in Intensive Care IV; ICU, intensive care unit; CVP, central venous pressure.

years (44.70 % women and 69.74 % Caucasians). The mean initial time of CVP measurement was 16.80 h after ICU admission, and the median CVP was 13.40 mmHg. One year after discharge, 7159 patients (63.69 %) survived, and 4082 patients (36.31 %) died of various causes; their clinical characteristics are presented in Supplemental Table S3. Our initial analysis focused on the temporal and dosage-dependent correlations between the early measurement of CVP and the one-year risk of mortality from any cause (Fig. 2A), 90 days (Fig. 2B), and 30 days (Fig. 2C). Interestingly, the associations were visualized as J-shaped after restricted cubic spline analysis. Estimated from the piecewise linear model, the nadir of risk occurred when the initial time of CVP measurement was 5 h, which was consistent across the above three models. Hence, we preliminarily defined CVP measurement within 5 h as early intervention. Stratified by this inflection point, 1913 (17.02 %) participants had early CVP measurement and 9328 (82.98 %) participants had delayed or no CVP measurements. Table 1 shows the baseline characteristics of the two groups. Compared to the group with delayed or no CVP measurement, participants in the early CVP measurement group were younger; had fewer women; higher SOFA and SAPSII scores; lower MAP; lower anion gap; different comorbidities; and more frequent use of mechanical ventilation, vasopressors, and diuretics.

Additionally, we also examined the possible association between the baseline CVP measurement and the one-year all-cause mortality risk using a restricted cubic spline model. A comparable J-shaped relationship is depicted in Supplemental Fig. S1. The lowest point of risk was observed at a baseline CVP of 8.8 mmHg. Mortality risk heightened when the baseline CVP was either below or above 8.8 mmHg.

3.2. Primary outcome

To further investigate the link between initial CVP assessments and the incidence of all-cause mortality over both short and extended durations in patients with severe heart failure, we generated Kaplan–Meier survival plots. Observations revealed that patients who underwent CVP measurement within the first 5 h exhibited an elevated likelihood of survival at the one-year mark (Fig. 3A), as well as at 90 days (Fig. 3B) and 30 days (Fig. 3C). To confirm the independent relationship, we conducted both univariate and multivariate Cox regression analyses (Table 2). Irrespective of whether the models were crude or adjusted multivariately, early CVP

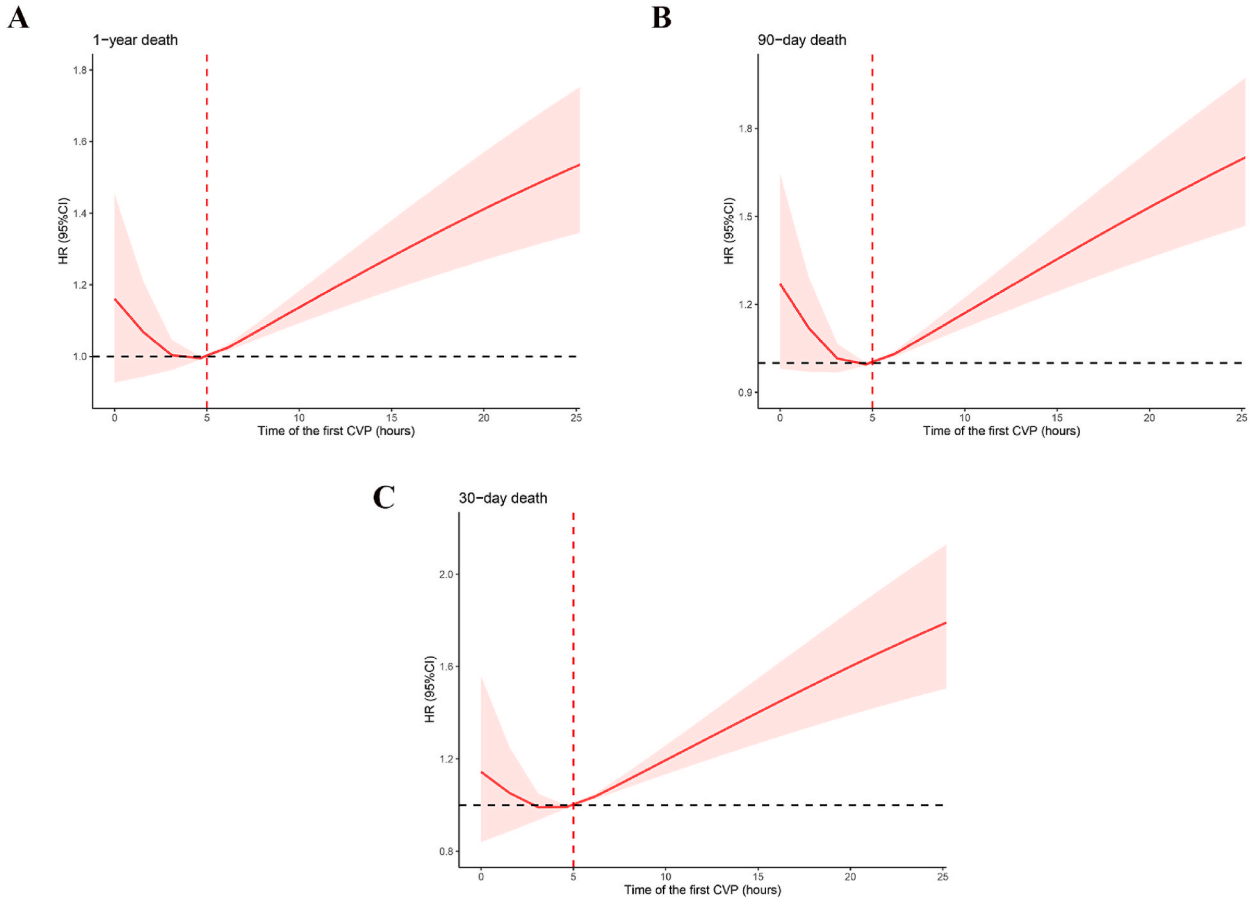

Fig. 2. Association between the initial time of CVP measurement and HR of 1-year (A), 90-day (B) and 30-day (C) all-cause death. CVP, central venous pressure; HR, hazard ratio.

Table 1
Comparison of the baseline characteristics between the groups of early CVP measurement and delayed or no CVP measurement before and after PSM.

Characteristics	Before PSM			After PSM		
	CVP>5h (n = 9328)	CVP≤5h (n = 1913)	SMD	CVP>5h (n = 1536)	CVP≤5h (n = 1536)	SMD
Demographics						
Age, years	75.74 (65.50–84.48)	72.11 (62.62–80.27)	0.24	72.26 (62.54–81.56)	72.32 (62.83–80.64)	0.01
Gender, n (%)			0.16			0.01
Male	5035 (53.98 %)	1181 (61.74 %)		941 (61.26 %)	935 (60.87 %)	
Female	4293 (46.02 %)	732 (38.26 %)		595 (38.74 %)	601 (39.13 %)	
Race, n (%)			0.17			0.03
White	6445 (69.09 %)	1394 (72.87 %)		1111 (72.33 %)	1095 (71.29 %)	
Black	932 (9.99 %)	107 (5.59 %)		87 (5.66 %)	93 (6.05 %)	
Asian	214 (2.29 %)	43 (2.25 %)		34 (2.21 %)	33 (2.15 %)	
Other	1737 (18.62 %)	369 (19.29 %)		304 (19.79 %)	315 (20.51 %)	
Disease severity scores						
SOFA	5.00 (3.00–7.00)	7.00 (5.00–10.00)	0.51	7.00 (5.00–10.00)	7.00 (5.00–10.00)	0.09
SAPSII	38.00 (31.00–47.00)	39.00 (32.00–49.00)	0.12	41.00 (33.00–50.00)	40.00 (32.00–50.00)	0.07
Signs						
Heart rate, beats/minute	83.16 (72.65–95.31)	82.10 (75.92–90.58)	0.07	82.37 (74.21–93.37)	82.19 (75.44–90.78)	0.04
MAP, mmHg	75.40 (69.20–82.80)	72.87 (68.42–77.45)	0.36	72.81 (67.77–77.93)	73.06 (68.49–77.77)	0.04
Respiratory rate, times/minute	19.69 (17.41–22.44)	18.22 (16.35–20.46)	0.41	18.55 (16.54–21.12)	18.40 (16.48–20.89)	0.01
Temperature, ∘C	36.76 (36.55–37.01)	36.72 (36.46–37.02)	0.06	36.74 (36.50–37.04)	36.72 (36.46–37.04)	0.01
Weight, kg	78.90 (65.50–95.10)	81.60 (68.10–96.00)	0.02	80.00 (67.78–96.02)	82.10 (68.57–97.00)	0.01
Urine output, L/d	1.47 (0.86–2.35)	1.61 (1.02–2.44)	0.10	1.47 (0.88–2.33)	1.55 (0.98–2.43)	0.03
SpO2, %	96.64 (95.21–97.96)	97.77 (96.62–98.78)	0.54	97.64 (96.32–98.74)	97.59 (96.47–98.63)	0.01
Laboratory tests						
Hemoglobin, g/dl	9.90 (8.40–11.50)	9.10 (8.00–10.50)	0.32	9.30 (7.90–10.90)	9.20 (8.00–10.70)	0.02
Platelets, $\times 10^9$/L	181.00 (132.00–241.25)	140.00 (107.00–188.00)	0.45	148.00 (108.00–203.00)	145.00 (109.00–197.00)	0.01
White blood cells, $\times 10^9$/L	9.20 (6.80–12.50)	10.40 (7.80–13.50)	0.12	9.85 (7.10–13.20)	10.20 (7.60–13.50)	0.02
Hematocrit, vol%	30.30 (25.80–35.10)	27.10 (24.10–31.50)	0.41	28.00 (24.20–33.12)	27.60 (24.40–32.40)	0.03
Anion gap, mmol/L	13.00 (11.00–16.00)	12.00 (10.00–14.00)	0.45	12.00 (10.00–15.00)	12.00 (10.00–14.00)	0.04
Bicarbonate, mmol/L	22.00 (19.00–25.00)	22.00 (20.00–24.00)	0.17	21.00 (19.00–24.00)	22.00 (19.00–24.00)	0.04
Blood urea nitrogen, mg/dL	25.00 (17.00–40.00)	20.00 (14.00–32.00)	0.27	22.00 (15.00–36.00)	21.00 (15.00–35.00)	0.04
Creatinine, mg/dL	1.10 (0.80–1.80)	1.00 (0.80–1.50)	0.18	1.10 (0.80–1.70)	1.10 (0.80–1.60)	0.02
Glucose, mg/dL	113.00 (95.00–139.00)	113.00 (98.00–132.00)	0.12	112.00 (96.00–136.00)	113.00 (98.00–134.00)	0.03
Sodium, mmol/L	137.00 (134.00–140.00)	137.00 (134.00–139.00)	0.01	137.00 (134.00–139.00)	137.00 (134.00–139.00)	0.01
Potassium, mmol/L	3.90 (3.60–4.30)	4.00 (3.70–4.40)	0.16	4.00 (3.60–4.40)	4.00 (3.60–4.40)	0.02
Calcium, mmol/L	8.30 (7.80–8.70)	8.20 (7.70–8.60)	0.15	8.10 (7.70–8.60)	8.10 (7.70–8.60)	0.01
Chloride, mmol/L	101.00 (97.00–104.00)	104.00 (100.00–107.00)	0.42	103.00 (99.00–106.00)	103.00 (99.00–106.00)	0.02
International normalized ratio	1.20 (1.10–1.50)	1.20 (1.10–1.40)	0.11	1.20 (1.10–1.40)	1.20 (1.10–1.40)	0.02
Prothrombin time, seconds	13.70 (12.20–16.30)	13.70 (12.50–15.40)	0.10	13.70 (12.40–15.70)	13.70 (12.50–15.70)	0.01
Activated partial thromboplastin time, seconds	29.90 (26.60–35.20)	29.50 (26.70–33.90)	0.10	30.35 (27.00–35.50)	29.60 (26.60–34.32)	0.05
Charlson Comorbidity Index	7.00 (6.00–9.00)	7.00 (5.00–8.00)	0.35	7.00 (5.00–9.00)	7.00 (5.00–9.00)	0.01
Comorbidities, n (%)						
Hypertension	2719 (29.15 %)	651 (34.03 %)	0.11	492 (32.03 %)	495 (32.23 %)	0.01
Pulmonary hypertension	745 (7.99 %)	151 (7.89 %)	0.01	126 (8.20 %)	117 (7.62 %)	0.02
Acute myocardial infarction	3110 (33.34 %)	632 (33.04 %)	0.01	559 (36.39 %)	537 (34.96 %)	0.03
Valvular heart disease	162 (1.74 %)	84 (4.39 %)	0.15	48 (3.12 %)	53 (3.45 %)	0.02
Cardiomyopathy	880 (9.43 %)	193 (10.09 %)	0.02	161 (10.48 %)	158 (10.29 %)	0.01
Atrial fibrillation	4661 (49.97 %)	1034 (54.05 %)	0.08	806 (52.47 %)	810 (52.73 %)	0.01
Stroke	547 (5.86 %)	45 (2.35 %)	0.18	38 (2.47 %)	44 (2.86 %)	0.02
Renal diseases	3636 (38.98 %)	617 (32.25 %)	0.14	540 (35.16 %)	530 (34.51 %)	0.01
Chronic obstructive pulmonary disease	3546 (38.01 %)	685 (35.81 %)	0.05	539 (35.09 %)	552 (35.94 %)	0.02
Liver diseases	875 (9.38 %)	183 (9.57 %)	0.01	157 (10.22 %)	163 (10.61 %)	0.01
Malignancy	1180 (12.65 %)	99 (5.18 %)	0.26	93 (6.05 %)	89 (5.79 %)	0.01
Diabetes mellitus	3838 (41.14 %)	747 (39.05 %)	0.04	600 (39.06 %)	609 (39.65 %)	0.01
Therapies, n (%)						
Mechanical ventilation	7929 (85.00 %)	1820 (95.14 %)	0.34	1446 (94.14 %)	1445 (94.08 %)	0.01
Extracorporeal membrane oxygenation	24 (0.26 %)	9 (0.47 %)	0.04	9 (0.59 %)	7 (0.46 %)	0.02
Assisted circulation	52 (0.56 %)	33 (1.73 %)	0.11	24 (1.56 %)	27 (1.76 %)	0.02
Percutaneous coronary intervention	339 (3.63 %)	37 (1.93 %)	0.10	43 (2.80 %)	37 (2.41 %)	0.02
Dialysis	372 (3.99 %)	51 (2.67 %)	0.07	56 (3.65 %)	47 (3.06 %)	0.03
Vasopressor	2963 (31.76 %)	1577 (82.44 %)	1.19	1239 (80.66 %)	1200 (78.12 %)	0.06
Inotrope	177 (1.90 %)	210 (10.98 %)	0.38	125 (8.14 %)	115 (7.49 %)	0.02

(*continued on next page*)

Table 1 (*continued*)

Characteristics	Before PSM			After PSM		
	CVP>5h (n = 9328)	CVP≤5h (n = 1913)	SMD	CVP>5h (n = 1536)	CVP≤5h (n = 1536)	SMD
Angiotensin-converting enzyme inhibitor	1154 (12.37 %)	238 (12.44 %)	0.01	161 (10.48 %)	165 (10.74 %)	0.01
Angiotensin receptor blocker	454 (4.87 %)	87 (4.55 %)	0.02	74 (4.82 %)	73 (4.75 %)	0.01
Beta-blocker	3909 (41.91 %)	937 (48.98 %)	0.14	657 (42.77 %)	695 (45.25 %)	0.05
Diuretic	4507 (48.32 %)	1122 (58.65 %)	0.21	823 (53.58 %)	864 (56.25 %)	0.05
First Care Unit			0.91			0.04
Cardiac care unit	3702 (39.69 %)	1531 (80.03 %)		1131 (73.63 %)	1155 (75.20 %)	
Medical intensive care unit	3789 (40.62 %)	284 (14.85 %)		299 (19.47 %)	283 (18.42 %)	
Other	1837 (19.69 %)	98 (5.12 %)		106 (6.90 %)	98 (6.38 %)	

CVP, central venous pressure; PSM, propensity score matching; SOFA, sequential organ failure assessment; SAPSII, simplified Acute Physiology Score II; MAP, mean arterial pressure; SpO2, peripheral capillary oxygen saturation; SMD, standard mean difference.

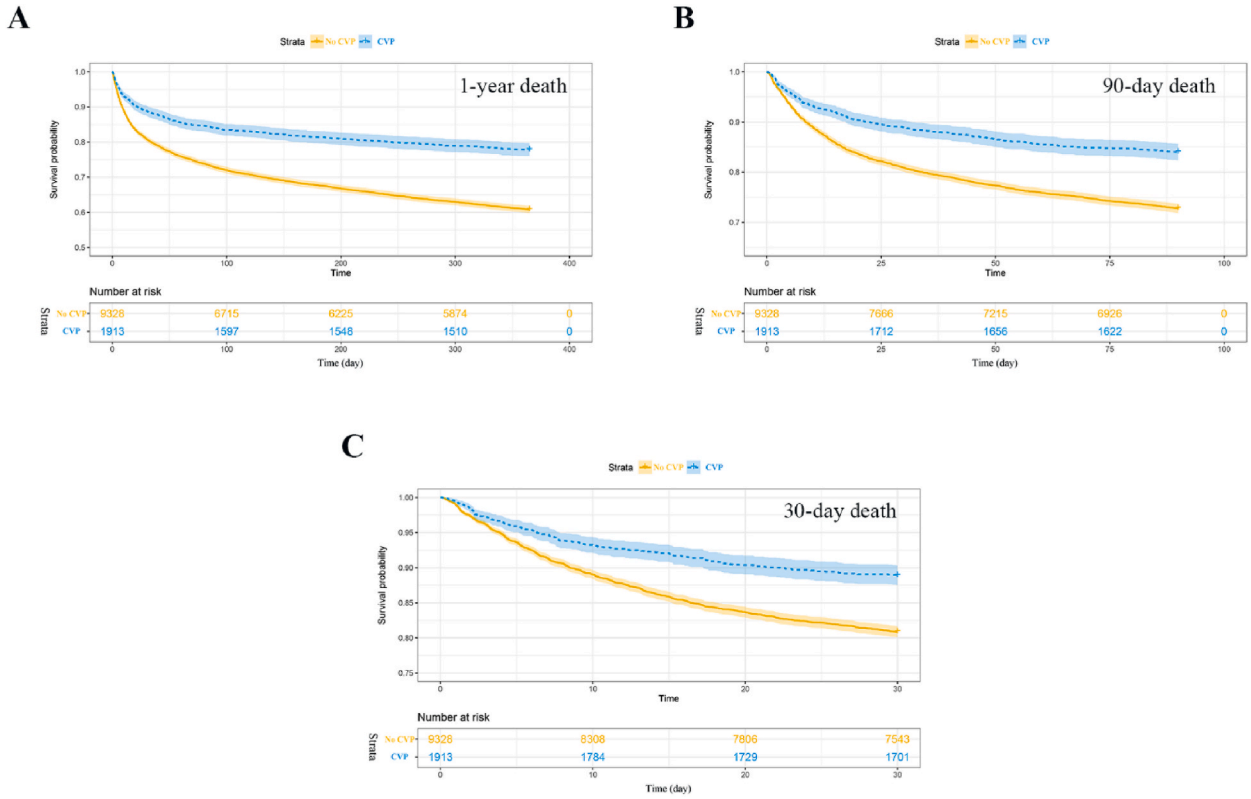

Fig. 3. Kaplan-Meier survival curves of patients with (blue) and without (yellow) early CVP measurement at 1-year (A), 90-day (B) and 30-day (C) follow-up. CVP, central venous pressure. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

measurement was robustly linked with lower mortality rates from all causes at 1-year, 90-day, and 30-day intervals. In Model II, patients who had an early CVP measurement experienced a decrease of 31 % (HR: 0.69; 95 % CI: 0.61–0.77, Fig. 4A), 30 % (HR: 0.70; 95 % CI: 0.62–0.80, Fig. 4B), and 33 % (HR: 0.67; 95 % CI: 0.57–0.78, Fig. 4C) in 1-year, 90-day, and 30-day all-cause mortalities, respectively. All the aforementioned models yielded statistically significant p-values ($P < 0.001$).

3.3. Subgroup analysis

The findings from the subgroup analysis are consolidated in Table 3. Across the subgroups of sex, race, initial CVP value, and SOFA and SAPSII scores, the correlation remained robust, with no significant interaction detected. Interestingly, the impact of early CVP measurement was more evident in the group aged less than 75 years compared to the group aged 75 years or older (HR: 0.58 vs. 0.77, *P* for interaction = 0.0170), although the correlation remained unchanged in both groups. Importantly, across all heart failure subtypes, early CVP measurement was significantly linked with lower all-cause mortality in patients with chronic heart failure (HR: 0.41; 95 %

Table 2
Association between early CVP measurement and all-cause mortalities in extended Cox regression models.

The initial time of CVP	Crude		Model I		Model II	
	HR (95 % CI)	*P*-value	HR (95 % CI)	*P*-value	HR (95 % CI)	*P*-value
1-year mortality						
>5	1 (ref)		1 (ref)		1 (ref)	
≤5	0.51 (0.46, 0.56)	<0.001	0.56 (0.51, 0.62)	<0.001	0.69 (0.62, 0.77)	<0.001
90-day mortality						
>5	1 (ref)		1 (ref)		1 (ref)	
≤5	0.55 (0.49, 0.62)	<0.001	0.62 (0.55, 0.69)	<0.001	0.71 (0.62, 0.80)	<0.001
30-day mortality						
>5	1 (ref)		1 (ref)		1 (ref)	
≤5	0.55 (0.48, 0.64)	<0.001	0.62 (0.54, 0.72)	<0.001	0.67 (0.57, 0.78)	<0.001

The variables were not adjusted in crude model. Age, gender, and race were adjusted in model I. Based on model I, model II further adjusted for SOFA, SAPSII, weight, heart rate, respiratory rate, mean arterial pressure, anion gap, chloride, urea nitrogen, malignancy, Charlson comorbidity index, mechanical ventilation, dialysis, vasopressor, and the type of ICU. CVP, central venous pressure; HR, hazard ratio; CI, confidence intervals; SOFA, sequential organ failure assessment; SAPSII, simplified Acute Physiology Score II.

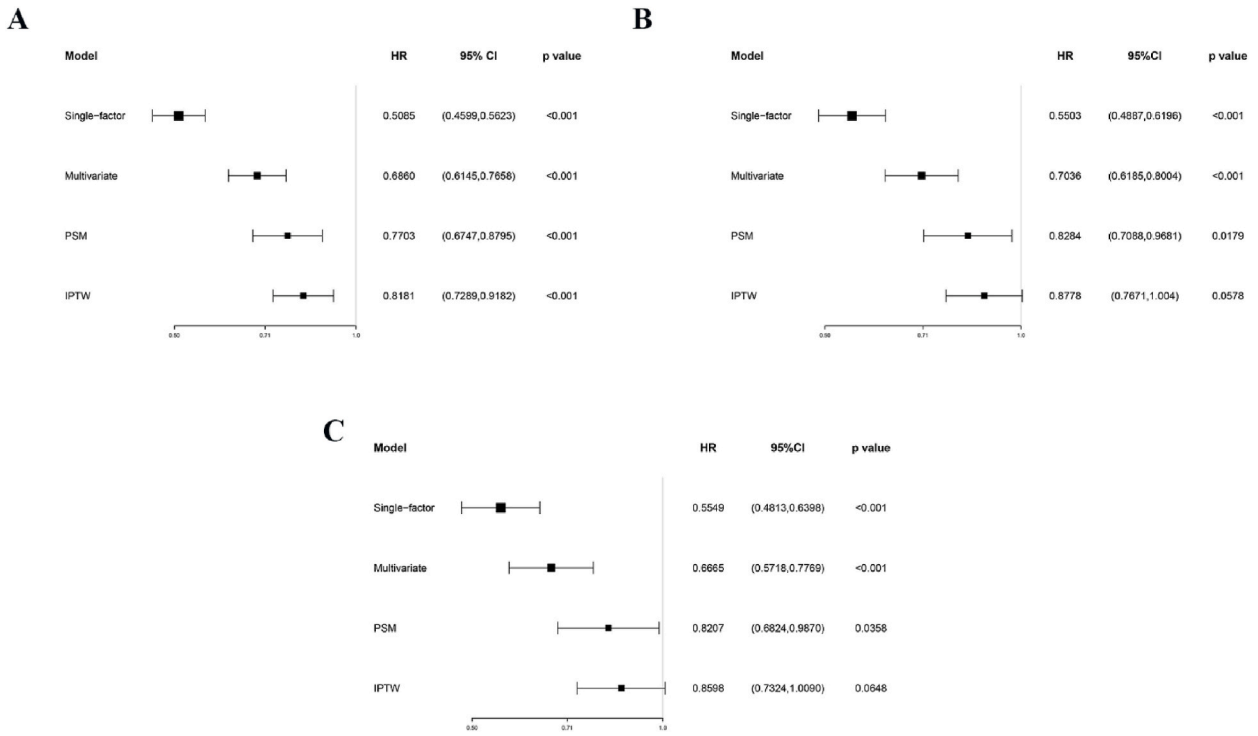

Fig. 4. Association between early CVP measurement and 1-year (A), 90-day (B) and 30-day (C) all-cause mortalities in different models. HR and 95 % CI in the cohorts of PSM and IPTW were calculated based on the multivariate model. PSM, propensity score matching; IPTW, inverse probability of treatment weighting; HR, hazard ratio; CI, confidence intervals; CVP, central venous pressure.

CI: 0.32–0.53) or acute-on-chronic heart failure (HR: 0.69; 95 % CI: 0.57–0.83), while no such correlation was observed in patients with acute heart failure (HR: 0.92; 95 % CI: 0.68–1.26). Patients with other forms of heart failure, such as rheumatic heart failure, were not further analyzed due to their inability to be classified into any of the aforementioned categories.

3.4. Outcomes after propensity score matching

To effectively balance confounding factors owing to stratification, we performed a 1:1 matched PSM analysis. Following propensity score matching (PSM), we established 1536 matched pairs of participants in the study, with the majority of covariates reaching equilibrium across the two cohorts (Table 1 and Supplemental Fig. S2). Kaplan–Meier survival plots revealed that subjects who underwent early CVP measurement exhibited prolonged survival durations and elevated survival probabilities, with the one-year mark showing the most pronounced difference (Supplemental Fig. S3). In addition, even after PSM and inverse probability of treatment weighting (IPTW) adjustments in multivariate model II, early CVP measurement's link to all-cause mortality persisted as statistically

Table 3
Subgroup analysis of the association between early CVP measurement and 1-year all-cause mortality.

Subgroups	N	Adjusted HR (95 % CI)	*P* value	*P* for interaction
Age				
<75 years	5613	0.58 (0.49, 0.70)	<0.0001	0.0170
≥75 years	5628	0.77 (0.67, 0.88)	0.0002	
Gender				
Male	6216	0.68 (0.58, 0.78)	<0.0001	0.7792
Female	5025	0.70 (0.59, 0.83)	<0.0001	
Race				
White	7839	0.70 (0.61, 0.79)	<0.0001	0.6998
Black	1039	0.70 (0.44, 1.11)	0.1266	
Asian	257	0.41 (0.16, 1.02)	0.0560	
Other	2106	0.69 (0.54, 0.87)	0.0023	
Initial CVP value				
<12 mmHg	1856	0.72 (0.59, 0.88)	0.0013	0.9525
≥12 mmHg	1982	0.73 (0.62, 0.87)	0.0003	
SOFA scores				
<5	4706	0.71 (0.53, 0.96)	0.0248	0.9112
≥5	6535	0.70 (0.62, 0.79)	<0.0001	
SAPSII scores				
<40	5988	0.63 (0.51, 0.78)	<0.0001	0.4286
≥40	5253	0.70 (0.61, 0.80)	<0.0001	
Subtypes of heart failure				
Acute heart failure	1235	0.92 (0.68, 1.26)	0.6054	0.0003
Chronic heart failure	2284	0.41 (0.32, 0.53)	<0.0001	
Acute-on-chronic heart failure	2924	0.69 (0.57, 0.83)	0.0001	
Unspecified subtypes	4798	0.51 (0.44, 0.60)	<0.0001	

CVP, central venous pressure; HR, hazard ratio; CI, confidence intervals; SOFA, sequential organ failure assessment; SAPSII, simplified Acute Physiology Score II.

significant, particularly concerning one-year mortality rates (Fig. 4). Table 4 summarizes the PSM-adjusted clinical outcomes of patients in detail. Among the secondary outcomes, early CVP measurement significantly shortened the duration of ICU stay and the duration of mechanical ventilation and vasopressor use in critically ill patients with heart failure. With regard to intravenous fluid volume during the first 3 days of ICU admission, interestingly, patients with early CVP measurement received more infusion on the first day (2.60 vs. 2.40 L, $p < 0.001$) and less infusion on the second day (0.93 vs. 1.07 L, $P < 0.001$) as well as the third day (0.90 vs. 1.00 L, $P = 0.015$).

3.5. Causal mediation analysis

Subsequent analysis utilizing causal mediation techniques was conducted to determine if the observed reductions in serum anion gap, CVP, and MAP acted as intermediary variables that contributed to the advantageous impact of early CVP assessment on the primary endpoint (Supplemental Fig. S4) When the serum anion gap was considered as a mediator, the total effect was −0.171 (95 % CI: −0.193, −0.150; $P < 0.001$); the average causal mediating effect was −0.029 (95 % CI: −0.034, −0.020; $P < 0.001$); the average direct effect was −0.142 (95 % CI: −0.163, −0.120; $P < 0.001$); and the proportion of beneficial effects mediated was 16.9 %. Hence, we infer that the serum anion gap partially mediated the beneficial effects of early CVP measurement. In comparison to the anion gap, the average causal mediating effect of CVP was −0.002 (95 % CI: −0.005, 0), and the proportion of beneficial effects mediated was merely 1.3 %. For MAP, the average causal mediating effect was 0.016 (95 % CI: 0.012, 0.020) and the proportion of negative effects mediated was 9.7 %.

Table 4
Primary and secondary outcomes after PSM.

Outcomes	CVP>5h (n = 1536)	CVP≤5h (n = 1536)	*P*-value
Primary outcome			
1-year mortality, %	32.10 % (493/1536)	25.59 % (393/1536)	<0.001
Secondary outcomes			
30-day mortality, %	16.15 % (248/1536)	13.48 % (207/1536)	0.037
90-day mortality, %	22.46 % (345/1536)	19.01 % (292/1536)	0.018
ICU duration, hours	82.00 (50.00–148.00)	75.00 (44.75–128.00)	<0.001
Volume of intravenous fluid on day 1, L	2.40 (1.37–3.70)	2.60 (1.65–3.80)	<0.001
Volume of intravenous fluid on day 2, L	1.07 (0.50–2.09)	0.93 (0.40–1.75)	<0.001
Volume of intravenous fluid on day 3, L	1.00 (0.45–2.00)	0.90 (0.40–1.75)	0.015
Mechanical ventilation-free days in 30 days	27.00 (24.00–28.00)	27.00 (25.00–28.00)	<0.001
Vasopressor-free days in 30 days	28.00 (27.00–29.00)	29.00 (27.00–29.00)	<0.001

PSM, propensity score matching; CVP, central venous pressure; ICU, intensive care unit.

4. Discussion

To our knowledge, this research is unprecedented in demonstrating a robust correlation between early CVP monitoring and enhanced clinical results. This includes a reduction in all-cause mortality at intervals of one year, 90 days, and 30 days, a shortened duration of ICU admission, and an augmentation in the number of days without the need for mechanical ventilation and vasopressors in patients with heart failure who are critically ill. Subgroup analysis revealed that early CVP measurement may provide additional beneficial effects for younger patients and those with chronic congestion status. Finally, we found that the serum anion gap partially mediated the beneficial effects of early CVP measurement through a causal mediation analysis.

Understanding the pathophysiological changes in the hemodynamics of patients with heart failure is crucial [15]. Although the benefits of hemodynamic monitoring in heart failure remain questionable [9,10], we believe that a reasonably timed intervention can make it a useful tool. Emerging evidence indicated that hemodynamic evaluation positively impacted the outcomes of patients with heart failure [16,17]. Hemodynamic change was an important metric used to study novel anti-heart failure drugs [18,19]. CVP serves as an indirect indicator of right ventricular preload and is influenced by multiple determinants, including volume status, cardiac output, blood pressure, intra-abdominal pressure, and mechanical ventilation [20]. These confounding factors complicate our understanding of CVP values in critically ill patients. However, from another perspective, CVP can comprehensively reflect hemodynamic status and help us make an overall judgment of the patients' volume status, intracardiac filling pressure, and peripheral perfusion. CVP should be evaluated in combination with clinical manifestations and cardiac output of patients to guide follow-up treatment.

Several studies have demonstrated the positive effect of early CVP measurements on the prognosis of critically ill patients [21–24]. In acute kidney injury, another clinical setting of volume imbalance, CVP measurement within 9 h was significantly associated with lower in-hospital mortality [21]. Observations indicate that recording CVP within a 24-h timeframe correlates with a decrease in 28-day mortality rates among patients with sepsis [22] and acute respiratory distress syndrome [23] cohorts. Patients who underwent cardiac surgery and had higher initial CVP values within 6 h of ICU admission exhibited elevated in-hospital mortality [24]. In this study, we demonstrated the benefit of measuring CVP within 5 h in critically ill patients with heart failure. Similar to the study by Yang et al. [21], we established a 5-h threshold by examining the correlation between the initial timing of central venous pressure (CVP) assessments and the overall risk of mortality from any cause. The 5-h threshold served as an inflection point when the risk began to rise. These findings were validated using multivariate Cox regression and sensitivity analyses. It is therefore justifiable to consider the assessment of CVP within a 5-h window as a prompt intervention for patients in critical condition suffering from heart failure. Nonetheless, further validation through prospective research is essential to confirm this observation.

Data analysis revealed that early CVP measurements had the strongest association with improved 1-year rather than with short-term all-cause mortality. In line with the findings of Chen et al. [22], early CVP measurement may lead to the optimization of treatment strategies to exert profound beneficial effects. Our findings intriguingly reveal that conducting CVP measurements early on significantly impacts the age-specific subgroups and different subtypes of heart failure. Early CVP measurement in patients under 75 years old provided more benefit than in those over 75 years old, which suggested that monitoring CVP and timely optimization of treatments were more effective for younger populations. For various subtypes of heart failure, the benefits of measuring CVP early were presented in chronic or acute-on-chronic heart failure rather than acute heart failure, which strengthened the sensitivity of CVP measurement to chronic congestion status. Compared with acute heart failure, monitoring hemodynamics in chronic congestion was safer and more effective [25–27]. Similar to our findings, management of chronic heart failure based on implantable hemodynamic monitoring systems could improve patient rehospitalization [16,17]. In brief, our data suggest more aggressive CVP measurements in younger patients and those with chronic congestion status.

The initial CVP value may influence the follow-up treatment and clinical outcomes in these patients. To explore the impact of initial CVP value, we stratified the patients into two groups with a threshold of 12 mmHg and re-performed Cox regression analysis. Early CVP measurement had an intimate connection with reduced 1-year all-cause mortality in both groups without a significant interaction. There was almost no difference in the initial CVP values between the early CVP measurement group and the delayed or no measurement group when the patients were stratified according to the timing of CVP monitoring. In addition, the initial CVP value was found to have a J-type association with 1-year all-cause mortality, with a nadir of 8.8 mmHg. This observation is easy comprehensible, as a low CVP indicates shock, while a high absolute value is directly linked to peripheral edema, ascites, and liver and kidney dysfunction [20,28].

Finally, we used a causal mediation analysis to explain the mechanism by which early CVP measurement improved patient outcomes. We first explored whether CVP or MAP could act as mediators; however, both metrics mediated limited effects, indicating that the primary effect of early CVP measurement was not achieved by reducing the CVP value or maintaining MAP value. Because of a significant amount of missing data, information on lactate levels was unavailable, and the anion gap was regarded as a surrogate indicator for lactate. Unexpectedly, we found that a reduction in the serum anion gap mediated a beneficial effect of 16.9 % in early CVP measurement. Why the anion gap could serve as a good mediator? Our research has established that a heightened serum anion gap is an independent prognostic indicator of adverse outcomes in patients critically ill with heart failure [29]. Hemodynamic instability leading to peripheral tissue hypoperfusion and metabolic acidosis is closely linked with a negative prognosis in heart failure patients [8,30–32]. The serum anion gap is positively correlated with the levels of acidic metabolites, such as lactate, and indirectly reflects tissue hypoperfusion. Next, we investigated why the anion gap declined in the group that underwent early CVP measurements. In contrast to their counterparts, the cohort undergoing prompt CVP assessment received a greater volume of intravenous fluids on the initial day post-ICU admission, yet markedly less on the subsequent second and third days. Fluid therapy, commonly administered by physicians to maintain tissue perfusion in severely ill patients, carries the potential for fluid overload. As per the principles of the Starling curve and the Guyton model of cardiac physiology, an elevated CVP—often a consequence of excessive fluid

administration—signals the halt of any further rise in cardiac output and a reduction in venous return; it also reflects severe microcirculatory congestive hypoxia, which is concerning [20,33,34]. Our data showed that the risk of fluid overload and microcirculatory congestive hypoxia in patients with early CVP measurements was appreciably lower than that in the other group. Consistent with this speculation, Chlabicz et al. [35] found that increased fluid volume was associated with higher mortality in patients with cold-wet (symptomatic hypotension and venous congestion) heart failure. Moreover, patients with early CVP measurements are more likely to receive active treatment with mechanical ventilation, ventricular assist devices, vasopressors, inotropes, diuretics, or beta-blockers. Notably, patients who underwent early CVP measurement exhibited better renal function, thus creating favorable conditions for the effective action of diuretics [36].

The study presents certain constraints. Initially, the diagnosis of heart failure relied on the 9th and 10th editions of the International Classification of Diseases, potentially broadening the inclusion criteria and raising concerns about diagnostic accuracy. Secondly, the absence of specific cause-of-death data precluded the exploration of a link between early CVP measurements and cardiovascular mortality in heart failure patients. Lastly, the left ventricular ejection fraction serves as a crucial stratification metric for heart failure; however, we could not include this in the main analyses because of missing data. The lack of data, such as NT-proBNP levels, made it difficult to cover all confounders. Fourth, we were unable to learn about the differences in laboratory tests and interventions the patients received before and after CVP measurement. This limitation renders our speculations regarding the benefits of early CVP measurement susceptible to challenge. It was difficult to fully elucidate the underlying mechanism between early CVP measurements and good outcomes in these patients. Finally, we drew these conclusions based on a single-center retrospective study. Multicenter prospective studies are required to further validate its clinical value.

5. Conclusions

Prompt initiation of CVP monitoring is closely linked to favorable outcomes in patients suffering from heart failure under critical care. This correlation appears particularly significant among younger individuals and patients experiencing persistent congestion. It is suggested that a decrease in the serum anion gap could play a role in facilitating these positive outcomes. However, these observations require confirmation through extensive prospective research in the future.

Ethics statement

The clinical subjects' identities were kept confidential, and the Beth Israel Deaconess Medical Center (BIDMC) exempted the necessity for informed consent. The researchers, upon application, successfully completed the "Protecting Human Research Participants" certification, which granted them authorization to utilize the MIMIC-IV database (Record ID: 43,449,634).

Funding

Our study was financially supported by the National Natural Science Foundation of China (82070055 and 82100071), the Hunan Provincial Natural Science Foundation (2024JJ6673 and 2024JJ6620), and the Fundamental Research Funds for the Central Universities of Central South University (2023ZZTS0550).

Data availability statement

Publicly available datasets were analyzed in this study. Data were available at https://physionet.org/content/mimiciv/2.0/after passing on the required courses and obtaining the authorization. We have gained access to the MIMIC-IV database (Record ID: 43,449,634).

CRediT authorship contribution statement

Benhui Liang: Writing – review & editing, Writing – original draft, Methodology, Investigation. **Yiyang Tang:** Methodology, Investigation. **Qin Chen:** Writing – review & editing, Methodology. **Jiahong Zhong:** Writing – review & editing, Methodology. **Baohua Peng:** Writing – review & editing, Methodology. **Jing Sun:** Writing – review & editing, Methodology. **Tingting Wu:** Writing – review & editing, Validation. **Xiaofang Zeng:** Writing – review & editing, Validation. **Yilu Feng:** Writing – review & editing, Validation. **Zaixin Yu:** Writing – review & editing, Validation. **Lihuang Zha:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to express sincere gratitude to the participants and staff of the MIMIC-IV database for their great

contributions.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e33599.

Abbreviations

Abbreviations	*Full name*
CVP	central venous pressure
ICU	intensive care unit
MIMIC-IV	Multiparameter Intelligent Monitoring in Intensive Care IV
SOFA	sequential organ failure assessment
SAPSII	Simplified Acute Physiology Score II
PSM	propensity score matching
HR	hazard ratio
CI	confidence intervals
BIDMC	Beth Israel Deaconess Medical Center
IPTW	inverse probability of treatment weighting
MAP	mean arterial pressure

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