Research on Clinical Biomarkers for Predicting the Risk of Death in Heart Failure

Kexin Li *

School of Life Sciences, University of Liverpool, Liverpool, England, L69 3BX

* Corresponding Author Email: kexinli0316@outlook.com

Abstract. Cardiovascular disease (CVD) is the leading cause of death globally, causing approximately 17 million deaths annually, with myocardial infarction and heart failure as the main lethal manifestations. Heart failure (HF) is defined as the inability of the heart to maintain adequate blood flow to meet the body's metabolic demands. This study aimed to identify mortality predictors in HF patients through clinical data analysis. This study statistically analysed 11 clinical characteristics of 299 HF patients. Serum creatinine and left ventricular ejection fraction (LVEF) were identified as key predictors of mortality risk. Serum creatinine levels were significantly higher ($P<0.001$) and LVEF was significantly lower ($P<0.001$) in patients who died compared to those who survived. Logistic regression analysis showed that each 1 mg/dL increase in serum creatinine level was associated with a 128.0% increase in the risk of death (OR = 2.28), whereas each 1% increase in LVEF was associated with an approximately 5.5% reduction in the risk of death (OR = 0.945). Additionally, serum creatinine showed a significant correlation with serum sodium levels ($P<0.05$), suggesting that disturbances in electrolyte homeostasis play an important role in the pathophysiology of HF. These findings validate serum creatinine and LVEF as reliable biomarkers for risk stratification of HF patients and provide an important foundation for early clinical intervention and individualised management. The findings highlight the interconnectedness of multiple organ systems, particularly the cardiorenal axis, in the progression of heart failure, and have important implications for understanding the pathological mechanisms of HF and developing therapeutic strategies.

Keywords: Heart failure, Mortality risk prediction, Serum creatinine, Left ventricular ejection fraction.

1. Introduction

Cardiovascular disease (CVD) encompasses a group of disorders affecting the heart and blood vessels, primarily including ischemic heart disease (such as myocardial infarction), cerebrovascular disease (stroke), heart failure, and peripheral arterial disease [1-2]. As the leading cause of death globally, CVD poses significant public health challenges. Among these conditions, heart failure (HF) stands out as a particularly critical concern due to its associated high rates of morbidity, hospital readmission, and mortality. Although interventions targeting modifiable risk factors (e.g., smoking, obesity) can reduce CVD incidence, the management of HF patients after diagnosis and prognostic prediction remains challenging. There is an urgent need for more accurate biomarkers to identify individuals at high risk of death.

Numerous studies have examined the association between multiple clinical characteristics and HF prognosis. Regarding demographic factors, advanced age has been identified as an independent predictor of death and readmission in HF [3]. Comorbid conditions significantly influence HF progression. Hypertension and diabetes serve not only as primary causes of HF but are also associated with poor prognosis when persistent [4]. Anaemia is common in patients with HF, and its occurrence is strongly associated with worsening renal function, an increased inflammatory state, and an elevated risk of death. Regarding laboratory biomarkers, studies are more intensive. Serum creatinine, a classic indicator for assessing renal function, is elevated to reflect decreased glomerular filtration rate and renal hypoperfusion, and is a strong predictor of readmission in HF [5]. Creatine kinase (CK), especially its cardiac isoform (CK-MB), primarily reflects myocardial injury, and its elevation is usually associated with short-term adverse outcomes after acute events [6]. Changes in platelet count and function may also be involved in inflammatory and thrombotic processes in HF and have some prognostic relevance, but their predictive value is relatively complex and may be influenced by other

factors. Among the structural and functional indices of the heart, left ventricular ejection fraction (LVEF) holds a central position. LVEF, defined as the volume of blood ejected from the left ventricle during each contraction as a percentage of its end-diastolic volume, is a key measure of the heart's systolic function and is critical for HF staging, therapeutic decisions, and prognostic assessment [7]. Notably, a study by Kwok et al. not only confirmed the prognostic value of LVEF but also demonstrated that each 1 mg/dL increase in serum creatinine level was significantly associated with a 27% increase in the risk of 30-day readmission for patients with HF, highlighting the role of multisystem interactions in HF prognosis.

2. Analysis of detection results based on Mann Whitney U test

All statistical analyses were performed using R statistical software (version 4.3.1), with statistical significance set at $\alpha = 0.05$. First, the assumption of normality was assessed using the Shapiro-Wilk test for all continuous variables [8]. The test results showed that all continuous variables significantly deviated from normal distribution (all $P < 0.05$); therefore, non-parametric tests were used for between-group comparisons of continuous variables.

Patients were categorised into survival and death groups based on death events. For non-normally distributed continuous variables, the Mann-Whitney U test (Wilcoxon rank sum test) was used to compare the distributional differences between the two groups, and the results were reported as the test statistic (U-value) and exact P-value [9]. For binary categorical variables, the chi-square test was used to compare the differences in frequency distributions between the two groups. If the expected frequency of any cell was less than 5, Fisher's exact test was used, and the results were reported as the chi-square value or the p-value for Fisher's exact test [10].

To further visualise the continuous variables that exhibited the most significant distributional differences in the between-group comparisons (p-values based on Mann-Whitney U-tests), box plots were drawn to present the median, interquartile range (IQR), and outlier profiles of the data.

To explore the association between between-group differences and the risk of death in greater depth, a univariate logistic regression model was constructed, with the event of death as a dichotomous dependent variable (death = 1, survival = 0), and the top two most significant variables in the between-group comparisons as independent variables. The aim was to quantify the strength of their associations with the risk of death. The results report the odds ratio (OR), 95% confidence intervals (95% CI), and corresponding p-values, and the model goodness-of-fit was assessed by the Hosmer-Lemeshow test .

Finally, Spearman's rank correlation coefficient (ρ) was calculated to explore patterns of association between potential predictors. This non-parametric method is suitable for assessing monotonic relationships between continuous and binary variables and does not require the data to satisfy the assumptions of normality or linearity [11]. All binary categorical variables were included in the analyses after they had been numerically recoded to 0/1, and the resulting correlation coefficient matrices were visualised using heat maps to visually present the strength and direction of the correlations between variables.

3. Results

3.1. Normality test

The results of the Shapiro-Wilk normality test showed (Table 1) that all continuous variables significantly deviated from normal distribution (all $p < 0.05$), so non-parametric tests were used for all subsequent analyses.

Table 1. Normality Test Results for Continuous Variables

Variable	Group	W Statistic	P Value	Distribution
Age	Death	0.9688881	2.20651e-02	Non-normal
Age	Survival	0.9796410	4.82762e-03	Non-normal
Serum creatinine	Death	0.6084221	1.28309e-04	Non-normal
Serum creatinine	Survival	0.5886272	9.58147e-22	Non-normal
Ejection fraction	Death	0.9265495	4.53496e-05	Non-normal
Ejection fraction	Survival	0.9199300	4.70484e-09	Non-normal
Serum sodium	Death	0.9582133	3.84052e-03	Non-normal
Serum sodium	Survival	0.9247749	1.08443e-08	Non-normal
Creatinine phosphokinase	Death	0.4392427	1.99253e-17	Non-normal
Creatinine phosphokinase	Survival	0.6277141	3.50906e-21	Non-normal
Platelets	Death	0.9713563	3.36292e-02	Non-normal
Platelets	Survival	0.8730402	5.14238e-12	Non-normal

Note: W statistic refers to the Shapiro-Wilk test statistic. P values < 0.05 indicate significant deviation from normality. All continuous variables showed non-normal distribution in both death and survival groups.

3.2. Between-group comparison of continuous variables

The results of the Mann-Whitney U test showed (Table 2) that among the six clinical parameters, serum creatinine and left ventricular ejection fraction were significantly different between the death and survival groups with large effect sizes. Additionally, age and serum sodium levels were also significantly different between the two groups, but with medium effect sizes and relatively limited clinical significance.

Table 2. Mann-Whitney U Test Results for Continuous Variables Between Death and Survival Groups

Rank	Variable	U Statistic	P Value	Effect Size	Significance
1	Serum creatinine	5298.0	1.58099e-10	0.370	Significant
2	Ejection fraction	13176.5	7.36824e-07	0.286	Significant
3	Age	7121.0	1.66752e-04	0.218	Significant
4	Serum sodium	12261.5	2.92756e-04	0.209	Significant
5	Platelets	10300.5	4.25585e-01	0.046	Non-significant
6	Creatinine phosphokinase	9460.0	6.84040e-01	0.024	Non-significant

Note: Variables are ranked by P value (lowest to highest). U statistic represents the Mann-Whitney U test statistic. Effect sizes are interpreted as small (0.1-0.3), medium (0.3-0.5), and large (≥0.5). P values < 0.05 indicate statistically significant differences between death and survival groups.

3.3. Between-group comparison of categorical variables

The results of the chi-square test showed (Table 3) that none of the five categorical variables differed significantly between the death and survival groups (all P > 0.05).

Table 3. Statistical Test Results for Categorical Variables Between Death and Survival Groups

Rank	Variable	Test Method	Test Statistic	P Value	Significance
1	High blood pressure	Chi-square	1.543461	0.2141034	Non-significant
2	Anaemia	Chi-square	1.042175	0.3073161	Non-significant
3	Smoking	Chi-square	7.331474e-03	0.9317653	Non-significant
4	Sex	Chi-square	0.000000	1.0000000	Non-significant
5	Diabetes	Chi-square	2.161684e-30	1.0000000	Non-significant

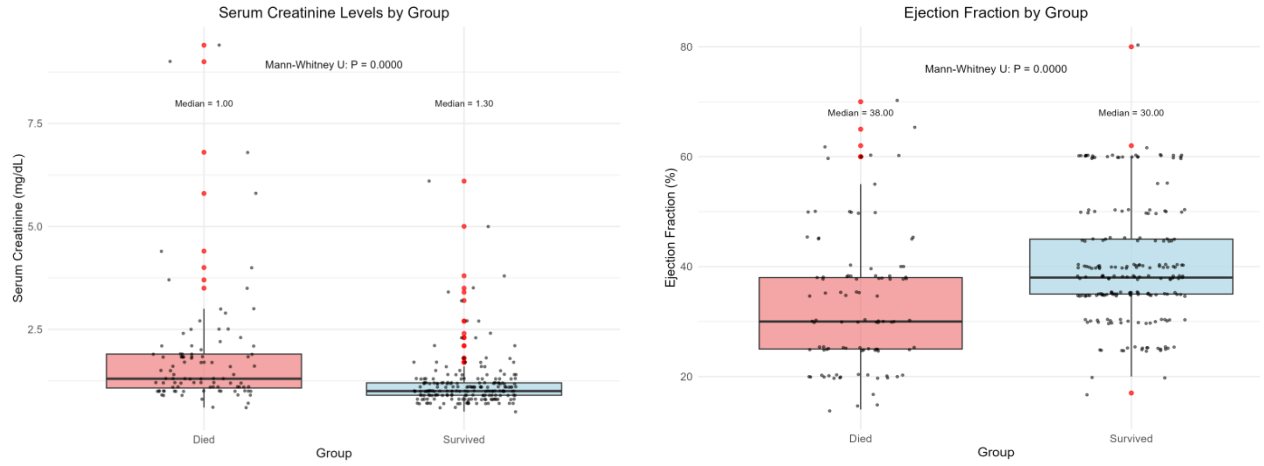
Note: Variables are ranked by P value (lowest to highest). Chi-square test was used for all categorical variables. Test statistics represent the chi-square statistic (χ^2). P values < 0.05 indicate statistically significant associations between categorical variables and mortality outcome. All categorical variables showed no significant association with mortality.

3.4. Box line plot presentation

Given that the Mann-Whitney U test showed significant differences in serum creatinine and LVEF between groups, their distributional characteristics were further demonstrated by box plots (Figure 1).

Serum creatinine analysis: Patients in the death group had significantly higher serum creatinine levels than those in the survival group (1.3 mg/dL vs 1.0 mg/dL, $P < 0.001$). The distribution of serum creatinine in the death group was more dispersed, with a median of 1.3 mg/dL, an interquartile range (IQR) of 1.08-1.9 mg/dL, and a mean value of 1.84 ± 1.47 mg/dL, suggesting that severe renal impairment was present in the deceased patients. In contrast, serum creatinine levels in the survival group showed a relatively centralised distribution with a median of 1.0 mg/dL and an IQR of 0.9-1.2 mg/dL, with a mean value of 1.18 ± 0.654 mg/dL.

LVEF analysis: Patients in the death group showed significantly lower LVEF than those in the survival group (30.0% vs 38.0%, $P < 0.001$). The distribution of LVEF in the survival group was relatively high, with a median of 38.0%, an IQR of 35.0-45.0%, and a mean of 40.3 ± 10.9%, with the majority of patients maintaining an ejection fraction above 35%. The LVEF was significantly lower in the death group, with a median of only 30.0%, an IQR of 25.0-38.0%, and a mean value of 33.5 ± 12.5%, and the distribution was more centred in the lower value range. Notably, the proportion of patients with ejection fraction below 30% was significantly higher in the mortality group, which is consistent with the clinically defined criteria of severely reduced ejection fraction.



(a) (b)

Figure 1. Distribution of Key Clinical Parameters by Survival Status

Box plots showing the distribution of (above) serum creatinine levels (mg/dL) and (below) left ventricular ejection fraction (%) stratified by survival status. Box plots display median (horizontal line), interquartile range (box), whiskers (1.5 × IQR), and individual data points. Red dots represent outliers. Statistical comparisons were performed using Mann-Whitney U test.

3.5. Univariate logistic regression analysis

Based on the significant results of between-group comparisons, univariate logistic regression analyses of serum creatinine and left ventricular ejection fraction were performed. Serum creatinine levels were significantly and positively associated with the risk of death (OR = 2.280, 95% CI: 1.598-3.455, $P < 0.001$), with a 128.0% increase in the risk of death per 1 mg/dL increase. Left ventricular ejection fraction was significantly and negatively associated with the risk of death (OR = 0.945, 95% CI: 0.921-0.968, $P < 0.001$), with a 5.5% reduction in the risk of death for each 1% increase.

Model fit assessment using the Hosmer-Lemeshow goodness-of-fit test suggested that the univariate model fit was suboptimal (serum creatinine model: $\chi^2 = 16.102$, $P = 0.013$; ejection fraction model: $\chi^2 = 28.665$, $P < 0.001$), suggesting that multivariate modelling is needed for better prediction of death risk.

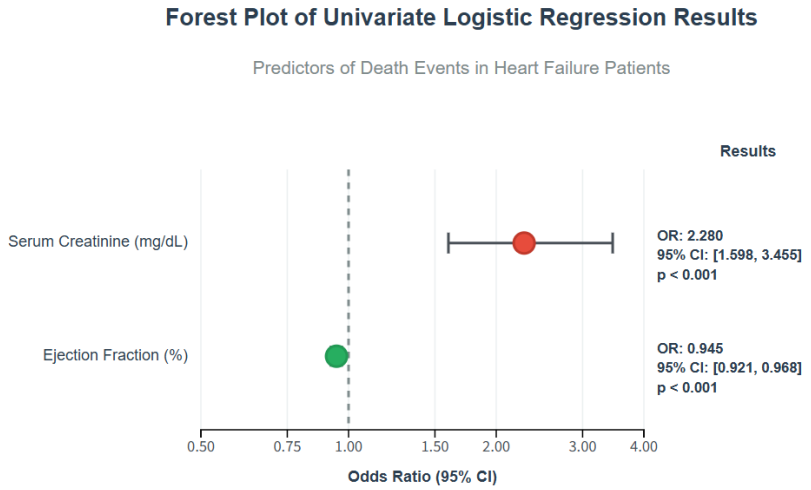


Figure 2. Forest Plot of Univariate Logistic Regression Results

As shown in Figure 2 forest plot showing odds ratios (OR) and 95% confidence intervals for serum creatinine and ejection fraction as predictors of death events. The vertical dashed line represents OR = 1.0 (no effect). Points to the right indicate increased risk (red), points to the left indicate decreased risk (green). Error bars represent 95% confidence intervals. All results are statistically significant ($p < 0.001$).

3.6. Results of correlation analysis

Spearman's rank correlation analysis revealed the pattern of associations between clinical parameters and correlations with death events. The correlation matrix (Figure 3) showed that serum creatinine was moderately negatively correlated with serum sodium ($r = -0.30$, $P < 0.001$), and age was weakly positively correlated with serum creatinine ($r = 0.27$, $P < 0.01$).

Analysis of correlations with death events (Figure 3 and Figure 4) showed that serum creatinine had the strongest correlation with death events ($r = 0.371$), followed by left ventricular ejection fraction ($r = -0.287$) and age ($r = 0.218$). Serum sodium was negatively correlated with death events ($r = -0.210$), and hypertension was weakly positively correlated with death events ($r = 0.079$). Of all the clinical parameters analysed, serum creatinine, left ventricular ejection fraction, age, serum sodium, and hypertension were the top five variables most significantly associated with death events.

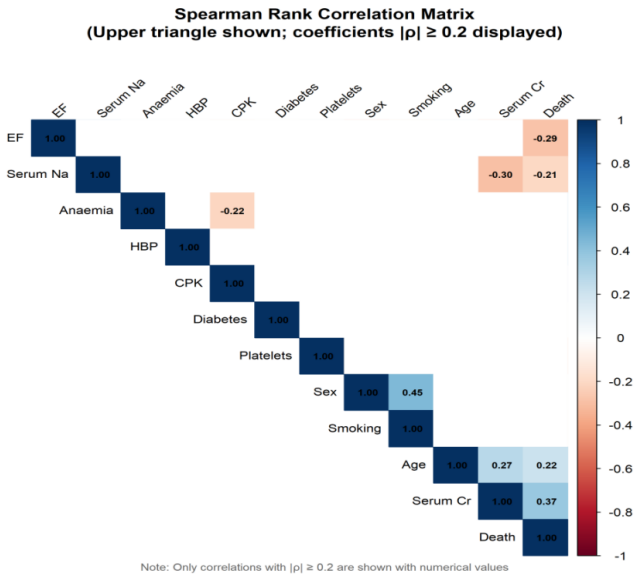


Figure 3. Spearman Rank Correlation Matrix of Clinical Variables in Heart Failure Patients.

Spearman correlation matrix of clinical variables. Upper triangle shown with coefficients $|\rho| \geq 0.2$ displayed. Blue: positive correlations; Red: negative correlations. Colour intensity indicates

correlation strength. Key abbreviations: EF = ejection fraction, HBP = high blood pressure, CPK = creatine phosphokinase, Serum Cr = serum creatinine.

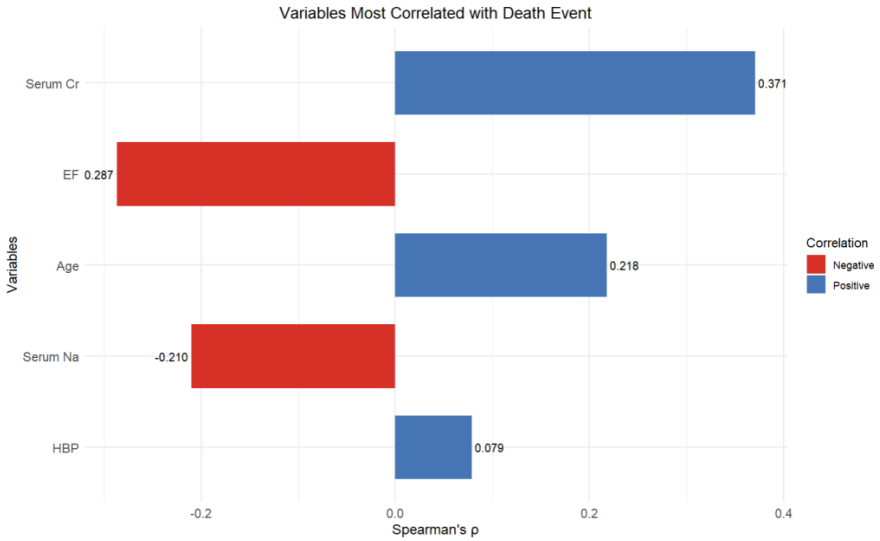


Figure 4. Correlation Analysis of Clinical Variables with Death Events in Heart Failure Patients

Spearman correlation coefficients between clinical variables and death events. Blue bars: positive correlations (risk factors); Red bars: negative correlations (protective factors). Variables ranked by correlation strength. ρ = Spearman's correlation coefficient.

4. Conclusions

This study identified serum creatinine and left ventricular ejection fraction (LVEF) as significant predictors of mortality risk in heart failure (HF) patients, based on comprehensive analysis of clinical data from 299 cases. Elevated serum creatinine and reduced LVEF were strongly associated with increased mortality, supporting the central role of cardiorenal axis dysfunction in HF progression.

These results are consistent with previous studies highlighting the prognostic significance of serum creatinine and LVEF in HF. Elevated serum creatinine reflects impaired renal perfusion and has been linked to increased mortality risk in several cohort [4]. Similarly, reduced LVEF remains a well-established marker of adverse outcomes, as supported by recent consensus guidelines [7].

Although other variables such as age and serum sodium showed statistical significance, their effect sizes and predictive strengths were limited. Categorical factors such as hypertension and diabetes did not reach significance in this sample, possibly due to variability in severity or control status.

The combined assessment of serum creatinine and LVEF offers a simple yet effective approach for early risk stratification. Future studies should consider multivariate modelling or machine learning to capture more complex interactions and enhance predictive performance, thereby facilitating more precise and individualised management strategies in clinical settings.

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