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Elevated serum pre-arrest cathepsin D concentrations are associated with higher mortality in in-hospital cardiac arrest

Taline Lazzarin^{1*}, Paula Schmidt Azevedo¹, Leonardo Antonio Mamede Zornoff¹, Sergio Alberto Rupp de Paiva¹, Filipe Welson Leal Pereira¹, Raquel Simões Ballarin¹ and Marcos Ferreira Minicucci¹

Cathepsin D (CatD) is a lysosomal enzyme implicated in ischemia–reperfusion injury, influencing apoptosis and inflammatory cytokine production [1]. It has been associated with cardiovascular diseases, atherosclerosis, heart failure, and acute conditions such as acute kidney injury (AKI) and pancreatitis [2]. However, its role in cardiac arrest (CA) remains unexplored. Therefore, this study aimed to evaluate the association between pre-arrest CatD levels, return of spontaneous circulation (ROSC), and mortality in in-hospital cardiac arrest (IHCA) patients.

An ambispective cohort study was conducted between August 2021 and April 2023 involving IHCA patients. Ethics approval was obtained (46,717,721.0.0000.5411), and the sample size was calculated using the CatD mean in patients with and without coronary artery disease [3], with a significance level of 5% and a power of 80%, resulting in a required sample size of 170 patients.

Eligible patients were those aged >18 years who suffered IHCA, underwent cardiopulmonary resuscitation (CPR), and had blood samples available within 48 h before CA. Only index CA events were considered. Data were extracted from electronic medical records,

including demographic, laboratory, and clinical variables. Serum pre-arrest CatD levels were measured using ELISA (Elabscience®) from blood samples available in the laboratory that were collected in the last 48 h before CA. The primary outcomes were sustained ROSC (≥ 20 min) and in-hospital mortality.

Statistical analyses were performed using SigmaPlot v12.0 and Stata v15.1. Continuous variables were analyzed using Student's t-test or Mann–Whitney test, while categorical variables were assessed using the χ^2 or Fisher's exact test. A receiver operating characteristic (ROC) curve was used to evaluate the predictive performance of pre-arrest CatD for in-hospital mortality. Due to the high mortality rate, penalized likelihood estimation with Firth logistic regression was applied, adjusting for clinically relevant and statistically significant variables. A significance level of 5% was adopted.

We included 199 patients (mean age 66.4 ± 15.5 years; 56.2% male). ROSC occurred in 43.7% of cases, while in-hospital mortality reached 95.0%, with only ten patients surviving. The cerebral performance category (CPC) scale classified 40% of survivors as CPC 1, 30% as CPC 2, and 30% as CPC 3, indicating that 70% had a good neurological outcome. Initial non-shockable rhythm, prolonged CPR, epinephrine use, elevated urea, and high pre-arrest CatD levels were associated with mortality (Table 1). Median pre-arrest CatD levels were significantly higher in non-survivors (39.9 pg/L) than in survivors (7.2 pg/L). ROC analysis demonstrated a strong association between pre-arrest

*Correspondence:

Taline Lazzarin
taline.lazzarin@unesp.br

¹ Internal Medicine Department, Botucatu Medical School, São Paulo State University (UNESP), Rubião Junior S/N, Botucatu, SP 18618-970, Brazil



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Table 1 Baseline characteristics and laboratory data of 199 patients with in-hospital cardiac arrest according to in-hospital mortality

Variable	In-hospital mortality		p value
	Yes (189)	No (10)	
Age (years)	69.0 (59.0–78.0)	61.5 (50.8–70.3)	0.101
Male gender, n (%)	103 (54.5)	9 (90)	0.060
Category, n (%)			
Medical	138 (73.0)	8 (80.0)	0.905
Surgery	51 (27.0)	2 (20.0)	
Initial rhythm, n (%)			
Nonshockable	175 (93.1)	7 (70.0)	0.044
Shockable	13 (6.9)	3 (30.0)	
Duration of CPR (min)	20.0 (10.0–30.0)	11.0 (7.0–17.0)	0.012
Medical history, n (%)			
Arterial hypertension	118 (62.4)	4 (40.0)	0.277
Diabetes	77 (40.7)	4 (40.0)	0.777
Smoking	39 (20.6)	5 (50.0)	0.073
Epinephrine (n° amp.)	5 (3–6)	3.5 (1–4.5)	0.043
Hemoglobin (g/dL)	11.0 (± 2.9)	12.7 (± 3.2)	0.130
Hematocrit (%)	34.0 (± 8.5)	38.6 (± 8.9)	0.160
Urea (mg/dL)	82.0 (46.0–139.0)	44.0 (32.0–80.0)	0.041
Creatinine (mg/dL)	1.5 (0.8–2.9)	0.9 (0.8–2.1)	0.297
Sodium (mmol/L)	138.0 (134.0–142.0)	138.0 (132.5–140.5)	0.417
Potassium (mmol/L)	4.3 (3.7–5.1)	4.0 (3.8–5.2)	0.990
Pre-arrest CatD (pg/L)	39.9 (13.0–50.2)	7.2 (3.7–16.0)	< 0.001

Data are expressed as the mean ± SD, median (25–75%) or percentage.
CPR = cardiopulmonary resuscitation; ROSC = return of spontaneous circulation;
CatD = cathepsin D

CatD and mortality (AUC 0.822; CI 0.7142–0.9302; $p < 0.001$ —supplementary Fig. 1) at a cutoff of 33.2 pg/L (sensitivity 56.6%, specificity 90%). Firth's penalized logistic regression confirmed that elevated pre-arrest CatD levels were an independent predictor of in-hospital mortality (supplementary Table 1), although no association with ROSC was observed.

This study is the first to demonstrate an association between elevated pre-arrest CatD levels and in-hospital mortality in IHCA patients. Unlike previous research that assessed biomarkers after CA, our analysis focused on pre-arrest samples collected within 48 h before CA, providing insight into pre-arrest deterioration rather than ischemia–reperfusion effects.

IHCA is a critical condition with poor outcomes [4]. Identifying early biomarkers could facilitate early intervention, prioritization of intensive care, and resource

allocation. Given its established role in cardiovascular and inflammatory diseases, pre-arrest CatD demonstrated strong prognostic potential in our study, with an AUC exceeding 0.8.

CatD has been implicated in various pathophysiological processes. In heart failure, elevated CatD levels have been associated with disease severity, higher mortality, and greater hospitalization rates. In atherosclerosis, CatD contributes to plaque instability. In AKI, CatD promotes tubular cell damage, while its inhibition has been shown to improve renal function and reduce apoptosis. In pancreatitis, CatD exacerbates inflammation and apoptosis. Furthermore, CatD plays a role in cancer aggressiveness, with antibody-mediated inhibition demonstrating therapeutic potential [2, 5]. Considering these findings, CatD may serve as a marker of poor health status preceding cardiac arrest.

Given the above considerations, we hypothesize that elevated pre-arrest CatD levels contribute to poor outcomes via apoptosis, protease activation, and inflammatory pathways, exacerbating post-CA injury. Notably, targeting CatD could represent a potential therapeutic strategy to mitigate adverse outcomes in critically ill patients, including those with IHCA.

This study has limitations, including its single-center design and high mortality rate. Additionally, information regarding the withdrawal of care was unavailable. Nevertheless, our findings provide novel insights into CatD as a potential prognostic biomarker in IHCA. This study demonstrates that increased serum pre-arrest CatD levels, measured within 48 h before IHCA, are independently associated with high in-hospital mortality. Future research should explore CatD's mechanistic role and potential therapeutic target to improve IHCA outcomes.

Abbreviations

CA	Cardiac arrest
IHCA	In-hospital cardiac arrest
CatD	Cathepsin D
AKI	Acute kidney injury
ROSC	Return of spontaneous circulation
CPR	Cardiopulmonary resuscitation
ROC	Receiver operating characteristic

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13054-025-05382-y>.

Additional file 1 Supplementary Fig. 1. ROC curve for the association between pre-arrest Cathepsin D level and in-hospital mortality (area under the ROC curve 0.822; CI 0.7142–0.9302; $p < 0.001$). Description of data: ROC curve analysis.

Additional file 2 Supplementary Table 1. Firth's penalized logistic regression for prediction of the in-hospital mortality in 199 patients with in-hospital cardiac arrest. Description of data: Firth's penalized logistic regression analysis.

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None

Author contributions

TL: conceptualization, methodology, formal analysis, writing—original draft; PSA, LAMZ, SARP, FWLP, RSB: methodology, formal analysis, writing—review & editing; MFM: conceptualization, methodology, writing—review & editing, visualization, supervision. All authors finalized the version submitted and agreed to be accountable for all aspects of the work.

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Availability of data and materials

Due to institutional policy, the datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request. No datasets were generated or analysed during the current study.

Declarations**Ethics approval and consent to participate**

This study was approved by the Ethics Committee of our Institution (46717721.0.0000.5411).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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