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Serum Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand and the Cardiovascular Disease Continuum: Insights from Hypertensive Urgencies and Acute Heart Failure Events

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Abstract: Background: Although TRAIL is a potent propapoptotic factor, its role in cardiovascular disease (CVD) remains unclear. This pilot exploratory study investigated serum TRAIL changes along the CVD continuum. We focused on two successive phases of this spectrum (systemic arterial hypertension and heart failure), with emphasis on acute cardiac events due to their immediate clinical significance. Methods: The study population included 90 age- and sex-matched patients hospitalized with hypertensive urgencies (HTUs) or acute decompensation episodes (ADHF). Key echocardiographic, endothelial, cardiometabolic, renal, and liver markers were assessed alongside TRAIL levels. Results: ADHF patients showed significantly elevated TRAIL concentrations, suggesting a progressive rise in TRAIL levels along the CVD continuum. They exhibited worse cardiac, hematologic, and renal profiles, with longer hospital stays and the cachexic phenotype. TRAIL correlated directly with asymmetric dimethylarginine, C-reactive protein, and admission potassium in ADHF patients. In hypertensive subjects, it correlated directly with asymmetric dimethylarginine and inversely with erythrocyte size variability. TRAIL may, thus, serve as a compensatory mechanism in HF, with potential as a biomarker for acute cardiovascular events. Conclusions: TRAIL dynamics provide valuable insights into CVD pathophysiology, particularly in acute settings, warranting further investigation to clarify its role in the broader context of apoptosis and cardiovascular health.

Keywords: TRAIL; cardiovascular disease; TNFSF 10; heart failure; hypertension; acute cardiac events

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1. Introduction

The cardiovascular disease (CVD) continuum is a concept illustrating the progression of vascular and heart diseases from modifiable risk factors and preclinical conditions to advanced stages and severe outcomes [1]. Systemic arterial hypertension (SAH) and heart failure (HF) are two important pieces of this puzzle [1] that can be seen as successive phases of this spectrum. SAH causes ventricular hypertrophy, which progresses further to HF through mechanisms such as ventricular dilatation and systolic dysfunction [2]. Aging promotes the progression of cardiac conditions along the CVD continuum via several mechanisms and effects, including arterial stiffening, reduced baroreceptor sensitivity, endothelial dysfunction, and altered diastolic function; thereby, the risk of CVD increases significantly in individuals over 60 years old [3]. Various biomarkers are used at different stages of the CVD continuum to reflect the underlying pathophysiology and meet

specific clinical needs [4]. For example, blood pressure monitoring is routinely used to assess and manage SAH [5]. N-terminal pro b-type natriuretic peptide (NT-proBNP) is employed to monitor cardiac stress and fluid status, important in managing both SAH and HF [6]. Asymmetric dimethylarginine (ADMA) offers insights into endothelial dysfunction throughout the CVD spectrum [7]. The relationship between apoptosis—a regulated form of cell death—and CVD is, however, less explored.

Altered apoptosis in SAH causes vascular remodeling [8]. These pathological changes promote arterial stiffness and resistance, thus elevating blood pressure and straining the heart [8]. Specifically, apoptosis has been reported in various hypertension models and is associated with cardiovascular remodeling processes like hypertrophy and hyperplasia [8,9] As CVD progresses to HF, apoptosis is pivotal for the loss of cardiac myocytes, reducing cardiac output and inducing pathological remodeling and cardiac fibrosis [10,11]. The tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is known as a major proapoptotic actor in cancer [12]. However, accumulating data provides evidence of its involvement in various non-cancerous diseases, including diabetes and CVD [13]. The interplay between TRAIL and the CVD spectrum involves complex interactions with vascular cells, inflammatory processes, and immune responses. Strong evidence supports the role of this protein in myocardial apoptosis [14]. There is also indication that TRAIL contributes to cardiac hypertrophy by promoting inflammatory pathways and apoptosis [15]. High levels appear to be protective in HF, whether with preserved or reduced ejection fraction [16,17]. Low TRAIL, by contrast, is linked to increased risks of rehospitalization and mortality in HF patients over up to five years [18]. However, the role of TRAIL in CVD is still not fully understood, and data on TRAIL levels across the CVD spectrum are sparse and vary significantly across different patient studies and conditions [19].

Here, we focus on serum TRAIL concentrations in acute phases; more precisely, we investigate hypertensive urgencies (HTUs) for SAH and episodes of acute decompensation (ADHF) for HF. In these critical conditions, TRAIL measurements can provide immediate and pertinent information on acute inflammatory responses and cellular stress [18]. While determining TRAIL levels during stable periods could be helpful for the ongoing management of SAH or HF, their immediate clinical significance is not as important as during acute episodes. It is, thus, expected that serum TRAIL concentrations during acute episodes offer more valuable insights related to immediate patient care and management strategies [19]. Our hypothesis, based on the data presented above, suggests potential differences in TRAIL levels measured during HTU and ADHF. We also assess important echocardiographic, endothelial, hematologic, cardiometabolic, renal, and liver health markers to gain new insights into the interactions between apoptosis and various body systems. For example, TRAIL not only influences atherosclerosis via lipid metabolism and inflammation [19,20], but it also interacts with metabolic and hepatic factors linked to central adiposity, increasing CVD risk [21]. In the renal context, the TRAIL-mediated modulation of cell dynamics under diabetic conditions supports its involvement in broader systemic interactions [22]. These data point to a complex network of interactions that is yet to be fully understood.

2. Materials and Methods

2.1. Design

This was a single-site, prospective, observational, exploratory, academic pilot clinical study without industry support. The study design involved a mixed-methods design; more precisely, a cross-sectional approach was complemented by longitudinal measurements to leverage the benefits of both observational methods. This hybrid model enabled us to efficiently collect baseline data on echocardiographic, endothelial, cardiometabolic, hematologic, renal, and hepatic indices, as well as temporal trajectories in selected renal parameters of cardiovascular significance. This approach is consistent with the strategies recommended by Korosteleva et al. (2008), who showed that mixed-method designs are effective for capturing complex health dynamics in resource-limited settings, as the case in exploratory pilot studies [23].

2.2. Setting

The Arad County Emergency Clinical Hospital ranks among the largest hospitals in Romania (with 1322 beds). Serving both local and adjacent areas, the hospital offers an extensive array of medical services across various specialties. Its facilities include a Level I trauma center, a contemporary emergency department, operating theaters, two intensive care units (ICUs), and a catheterization laboratory. Furthermore, it hosts a regional air ambulance service, complete with a dedicated helipad [24].

2.3. Protocol

This investigation was performed at the Department of Cardiology from the Arad County Emergency Clinical Hospital (Arad, Romania) [24] in accordance with the Declaration of Helsinki (1964) and its subsequent amendments. Ethical approval was granted by the Institutional Ethics Committees from the aforementioned hospital (approval No. 23/13.12.2018) and "Vasile Goldiș" Western University of Arad, Romania (approval No. 141/01.03.2019). Patients participating in this research were selected from a broader cohort of individuals hospitalized over a six-month period of time, from August 2020 to February 2021. Informed consent was obtained and signed by all patients or their caregivers. All patient identification information was kept strictly confidential.

The study inclusion criteria were patients aged 18 years or older who had signed informed consent, as well as a diagnosis of SAH. The latter included a documented history of systemic arterial hypertension, having been admitted to the emergency department for HTU, systolic blood pressure (BP) >180 mmHg, and/or diastolic BP > 120 mmHg without acute target organ damage. For HF, patients with a clinical diagnosis of heart failure who were admitted for ADHF characterized by worsening shortness of breath, edema, or other symptoms indicating acute HF were included. The primary exclusion criteria were having undergone major cardiovascular surgery or intervention (e.g., coronary artery bypass graft, stent placement) within the last 60 days; severe infections that could affect inflammatory markers; active malignancy or history of cancer treatment within the past 5 years; chronic kidney disease requiring dialysis; advanced liver disease such as cirrhosis or acute hepatic failure; use of immunosuppressive therapy or corticosteroids; recent initiation (within 30 days) or change in dosage of medications known to significantly affect cardiovascular, renal, or hepatic function; pregnancy; and a history of drug or alcohol abuse that could interfere with adherence to study protocols. The diagnoses of the conditions were made through clinical assessment and diagnostic tests, including blood chemistry for serum creatinine and urea, electrocardiography, computed tomography, and ultrasound imaging when required. Hypertensive crises were categorized as hypertensive urgency if no end-organ damage was detected. Cases with end-organ damage were identified as hypertensive emergency and were excluded from the study.

2.4. Measurements

First, 158 cardiac patients were pre-enrolled on a rolling "first come, first served" criterion if they were admitted to the Arad County Emergency Clinical Hospital from the Emergency Department (ED) due to hypertensive urgencies or episodes of acute decompensated HF. All measurements were conducted using validated and calibrated devices to ensure consistency across all data points. Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were recorded at ED triage. Echocardiography was conducted as soon as possible after admission to the hospital (within the first 1 to 2 h after arrival) to assess the patient's baseline cardiac condition. Ejection fraction (EF), left atrial diameter (LAD), left ventricle diameter (LVD), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and interventricular septum thickness (IVSWd) were measured because these metrics are crucial indicators of cardiac health. Thus, EF is considered a key indicator of cardiac performance. Enlarged LAD indicates chronic pressure overload and atrial fibrillation. LVD and LVEDV are associated with ventricular hypertrophy/dilatation and increased preload. Elevated LVESV reflects

worsening heart failure. Increased IVSd is a sign of hypertension-related hypertrophic changes [6,7,11].

Blood samples (50 mL) were collected within the same time frame to capture the effects of acute hypertensive crises or acute decompensation episodes [25]. The key hematological indices measured included erythrocyte sedimentation ratio (ESR), C-reactive protein (CRP), absolute leukocyte count (ALC), absolute neutrophil count (ANC), platelet-related parameters (RDW-CV, RDW-SD), and hemoglobin. ADMA and NT-proBNP were used, respectively, as biomarkers for endothelial dysfunction and cardiac stress [25,26]. Indices of renal function included serum creatinine, glomerular filtration rate (GFR), serum urea, serum uric acid, serum sodium, and serum potassium. The cardiometabolic parameters measured were total cholesterol, LDL, HDL, triglycerides, random glucose, and glycated hemoglobin (HbA1c), while liver function was evaluated using aspartate transaminase (AST) and alanine transaminase (ALT).

Additional blood samples (20 mL) were collected at discharge to determine serum creatinine, potassium, and sodium levels. Measuring these parameters at both admission and discharge is critical for patients hospitalized due to hypertensive crises or acute decompensation episodes. This monitoring helps to determine kidney function, detect electrolyte imbalances, and evaluate treatment effectiveness, thereby preventing complications such as arrhythmia and worsening HF [26]. Biochemical analyses were run at the Arad County Emergency Clinical Hospital, except for ADMA and TRAIL measurements, which were conducted at the "Vasile Goldiș" Western University of Arad. All analyses were conducted in triplicate, and only the mean values were considered.

For ELISA analysis, 20 mL of the initial blood samples were incubated at 25 °C for 2 h in test tubes, followed by centrifugation at 1000× g for 15 min. The resulting serum was stored at −20 °C until analysis. After defrosting, half of the serum was used to assess ADMA levels, and the other half was used to determine TRAIL concentrations. ADMA was measured using the Human ADMA ELISA Kit (Cusabio, Wuhan, China), as detailed in our previous work [26]. TRAIL was quantified using the human TRAIL PicoKineTM ELISA kit (Boster Bio, Pleasanton, CA, USA) and a microplate reader, Stat Fax 4200 (Awareness Technology, Palm City, FL, USA) [27]. To accurately quantify ADMA and TRAIL, standard curves were generated by plotting the $\log_{10}$-transformed concentrations against the corresponding optical densities of the positive controls. The ELISA calibration curves demonstrated coefficients of determination (R^2) above 0.97. All determinations were performed in triplicate, with coefficients of variability being 7.8% for the Human ADMA ELISA Kit and 8.3% for the TRAIL PicoKineTM ELISA kit.

To ensure a homogeneous study group, the patients were selected from the initial cohort of 158 individuals after careful age and sex matching. This was crucial to minimizing bias and providing accurate results in pilot, exploratory studies [23]. We also collected sociodemographic data (sex, age, origin, smoking status) and data on the presence of diabetes, tachycardia, and renal dysfunction in the study population. New diabetes was defined as HbA1c above 6.5% and/or fasting plasma glucose greater than 125 mg/dL and/or random plasma sugar exceeding 200 mg/dL [26]. Tachyarrhythmia was defined as a heart rate of at least 100 beats/min [28]. Renal dysfunction was diagnosed based on a GFR less than 60 mL per minute per 1.73 m^2 of body-surface area [28].

2.5. Data Analysis

Data were analyzed with the Statistica version 8 software (StatSoft Inc., Tulsa, OK, USA). The homogeneity of patients hospitalized with HTU or ADHF in terms of age and sex was determined with a Mann–Whitney U test and a Chi-square (χ^2) test, respectively. Intergroup comparisons for the other categorical variables (proportions) and cross-sectional continuous variables (datasets containing a single set of measurements) were conducted using the same methodology. For intra-group comparisons of longitudinal continuous variables (multiple sets of measurements), Wilcoxon signed-rank tests were used. We employed nonparametric tests instead of parametric tests, as this approach is favored in

pilot, exploratory studies primarily because of its flexibility with assumptions, suitability for small sample sizes, robustness against outliers and skewed distributions, capability to handle various types of data, and conservative nature [29]. These characteristics help to ensure that the findings of pilot studies are valid and reliable, paving the way for more comprehensive follow-up research [29,30]. For each stratum of patients, Pearson's correlations between TRAIL and the other continuous variables were conducted. Correlational analysis is typically used in pilot, exploratory investigations to uncover initial insights and guide further research [31,32]. It helps in identifying potential relationships, generating hypotheses, and building preliminary models that can be refined and tested in subsequent studies [33]. The strength of these associations was described as follows: very weak, $r = 0.00–0.09$; weak, $r = 0.10–0.29$; moderate, $r = 0.30–0.49$; strong, $r = 0.50–0.69$; and very strong, $r = 0.70–1.00$ [34]. Two-sided p-values < 0.05 were considered significant [35].

3. Results

3.1. Health Profiles in HTU and ADHF

After age and sex matching, 45 patients with HTU and 45 patients with ADHF were selected to be included in this pilot study. Their sociodemographic characteristics are given in Table 1. No significant inter-group differences existed with respect to sex distribution, area of origin, smoking status, diabetes, or presence of tachyarrythmia (Table 1). However, ADHF patients showed a significantly higher incidence of renal dysfunction compared to those presenting to the ED with HTU (Table 1).

Table 1. Sociodemographic characteristics and health conditions in patients with ADHF or HTU.

Characteristic	Strata	HTU Patients	ADHF Patients	p
Sex	Male	24 (53.34%)	28 (62.22%)	0.521
	Female	21 (46.66%)	17 (37.78%)	
Origin	Rural	30 (66.67%)	23 (51.12%)	0.198
	Urban	15 (33.33%)	22 (48.88%)	
Smoking status	Yes	18 (40%)	12 (26.67%)	0.263
	No	27 (60%)	33 (72.32%)	
Diabetes	Yes	16 (35.56%)	23 (51.12%)	0.137
	No	29 (64.44%)	22 (48.88%)	
Tachyarrythmia	Yes	17 (37.78%)	23 (48.78%)	0.212
	No	28 (63.22%)	22 (50.22%)	
Renal dysfunction	Yes	12 (26.67%)	26 (57.77%)	<0.001 ***
	No	33 (73.33%)	19 (42.23%)	

Data are shown as absolute values with the corresponding percentages in parentheses. Marked values (*) show significant differences compared to HF patients (χ^2 tests, ***—$p < 0.001$, **—$p < 0.01$, *—$p < 0.05$).

Median values (with lower and upper quartiles) for age, SBP, DBP, LAD, LVD, LVEDV, LVESV, IVSd, ADMA, NT-proBNP, ESR, CRP, ALC, ANC, RDW-CV, RDW-SD, hemoglobin, GFR, serum urea, serum uric acid, random glucose, HbA1c, total cholesterol, LDL, HDL, triglycerides, AST, and ALT are given in Table 2. The measured values for length of hospital stay, serum TRAIL, HR, and EF are illustrated in Figure 1a–d, and those for serum creatinine (at admission and discharge), serum sodium (at admission and discharge), and serum potassium (at admission and discharge) in Figure 2a–c.

Table 2. Measured values for selected parameters in patients with ADHF or HTU.

Characteristic	ADHF Patients	HTU Patients	Reference Range	*p*
Age (years)	70 (63; 79)	70 (62; 77)		0.257
SBP (mm Hg)	140 (130; 150)	150 (140; 160)	90–130	0.303
DBP (mm Hg)	80 (73; 90)	80 (75; 90)	60–80	0.659
ADMA (ng/mL)	111 (60; 240)	105 (80; 219)		0.941
NT-proBNP (pg/mL)	5136 (2060; 8400)	1570 (580; 5600)		0.064
LAD (mm)	43 (40; 80)	41 (36; 44)	25–53	0.093
LVD (mm)	51 (43; 58)	47 (45; 59)	39–59	0.216
LVEDV (mL)	125.5 (94; 173)	120.5 (82.5; 120)	46–150	0.619
LVESV (mL)	77 (55.5; 111.3)	55 (42; 82.5)	14–61	0.145
IVSd (cm)	1.16 (1; 1.3)	1.2 (1; 1.3)	0.6–1.2	0.792
ALC (cells/µL)	5365 (4110; 6139)	6125 (5400; 7139)	4000–11,000	0.013 **
ANC (cells/µL)	6175 (3820; 7400)	4670 (3350; 6425)	2500–7500	0.187
RDW-CV (%)	15.05 (14.1; 16.6)	14.2 (13.2; 15.15)	11.5–15.4	0.002 ***
RDW-SD (fL)	46.4 (44.3; 50.55)	43.90 (41.15; 47.95)	39–46	0.006 **
Hemoglobin (g/dL)	12.8 (11.6; 13.8)	14.8 (13; 15.2)	12–18	<0.001 ***
ESR (mm/h)	30 (24; 43)	26 (18;42)	0–30	0.580
CRP (mg/L)	13 (5; 42)	12 (1; 61)	<10	0.363
Random glucose (mg/dL)	133 (112; 170)	119 (99; 161)	<200	0.229
Hba1C (%)	6.9 (6; 7.80)	7.9 (6; 8.6)	<6.5	0.122
GFR (mL/min)	67.82 (47.94; 88.64)	77.69 (96.85; 102.5)	>60	0.173
Serum urea (mg/dL)	53.67 (44; 68)	37 (31; 65.8)	<49	0.007 **
Serum uric acid (mg/dL)	8.2 (7.2; 10.4)	7.70 (5.5; 10.3)	3–7	0.463
Total cholesterol (mg/dL)	147.8 (117;175)	175 (128; 200)	<200	0.092
LDL (mg/dL)	88.3 (71; 120)	118 (79; 135)	<130	0.109
HDL (mg/dL)	41 (34; 50)	40.35 (35; 48.75)	>40	0.885
Triglycerides (mg/dL)	98 (80; 131)	118 (98; 220)	<150	0.017 *
AST (UI/L)	28.5 (20; 40)	25.3 (19; 38)	5–56	0.621
ALT (UI/L)	24 (17.45; 35)	25.5 (16.5; 54.5)	9–40	0.798

Data are given as median values with lower and upper quartiles (in parentheses). Marked values (*) indicate significant differences compared to low-ADMA patients (Mann–Whitney U tests, ***—$p < 0.001$, **—$p < 0.01$, *—$p < 0.05$).

In patients hospitalized with either HTU or ADHF, median SBP, CRP, Hba1C, and serum uric acid were above the normal range. Median LVESV was above the normal range in the latter strata. The median values corresponding to the other continuous variables were within normal limits.

Statistical analysis revealed no age differences between individuals hospitalized with HTU and ADHF (Table 1). The latter category of patients spent significantly more time in the hospital (Figure 1a; Mann–Whitney U test, 5 days (4; 7) vs. 4 days (2; 6), $p = 0.017$) and exhibited significantly elevated TRAIL levels (Figure 1b; Mann–Whitney U test, 96 ng/mL (76; 118) vs. 79.5 pg/mL (69.5; 86), $p = 0.024$). ADMA concentrations in the two strata were, however, similar (Table 2). No significant inter-group differences were found with respect to SBP and DBP (Table 2). HF patients displayed a significantly faster HR (Figure 1c; Mann–Whitney U test, 90 bpm (72; 110) vs. 80 bpm (72; 90), $p = 0.007$), but a significantly lower EF (Figure 1d; Mann–Whitney U test, 40% (30; 50) vs. 55% (45; 60), $p < 0.001$). In contrast, the other cardiovascular and echocardiographic variables showed comparable values (Table 1).

Serum creatinine in ADHF patients was significantly elevated at discharge versus admission (Figure 2a; Wilcoxon signed-rank test, 1.025 mg/dL (0.88; 1.03) vs. 1.16 (0.89; 1.40), $p = 0.022$). The measured values in HTU patients showed, by contrast, a significant reduction at hospital dismissal (Figure 2a; Wilcoxon signed-rank test, 1.1 mg/dL (0.87; 1.26) vs. 0.97 (0.80; 1.24), $p = 0.028$). Serum urea was significantly elevated in ADHF compared to HTU (Table 2), but no significant differences were found for serum uric acid (Table 2). In addition, no differences were detected between the levels of serum sodium measured at admission and discharge in individuals hospitalized with ADHF (Figure 2b; Wilcoxon signed-rank test, 140 mmol/L (137; 142) vs. 138.5 (135; 141), $p = 0.835$). Similar results were

obtained for HTU (Figure 2b; Wilcoxon signed-rank test, 140 mmol/L (137; 142) vs. 140 (134; 141), $p = 0.928$). In addition, no significant differences existed for serum potassium at discharge vs. admission in HF patients (Figure 2c; Wilcoxon signed-rank test, 4.3 mmol/L (4; 4.7) vs. 4.15 (4; 4.4), $p = 0.125$r) or hypertensive patients (Figure 2c; Wilcoxon signed-rank test, 4.1 mmol/L (3.6; 4.3) vs. 4.2 (4.1; 4.3), $p = 0.845$).

The parameters of glycemic control in ADHF and HTU patients were comparable (Table 2). Similar results were obtained for lipid markers (Table 2), except tryglicerides, which exhibited significantly lower values during ADHF than during HTU (Table 2). Transaminase concentrations were also similar between the two strata (Table 2).

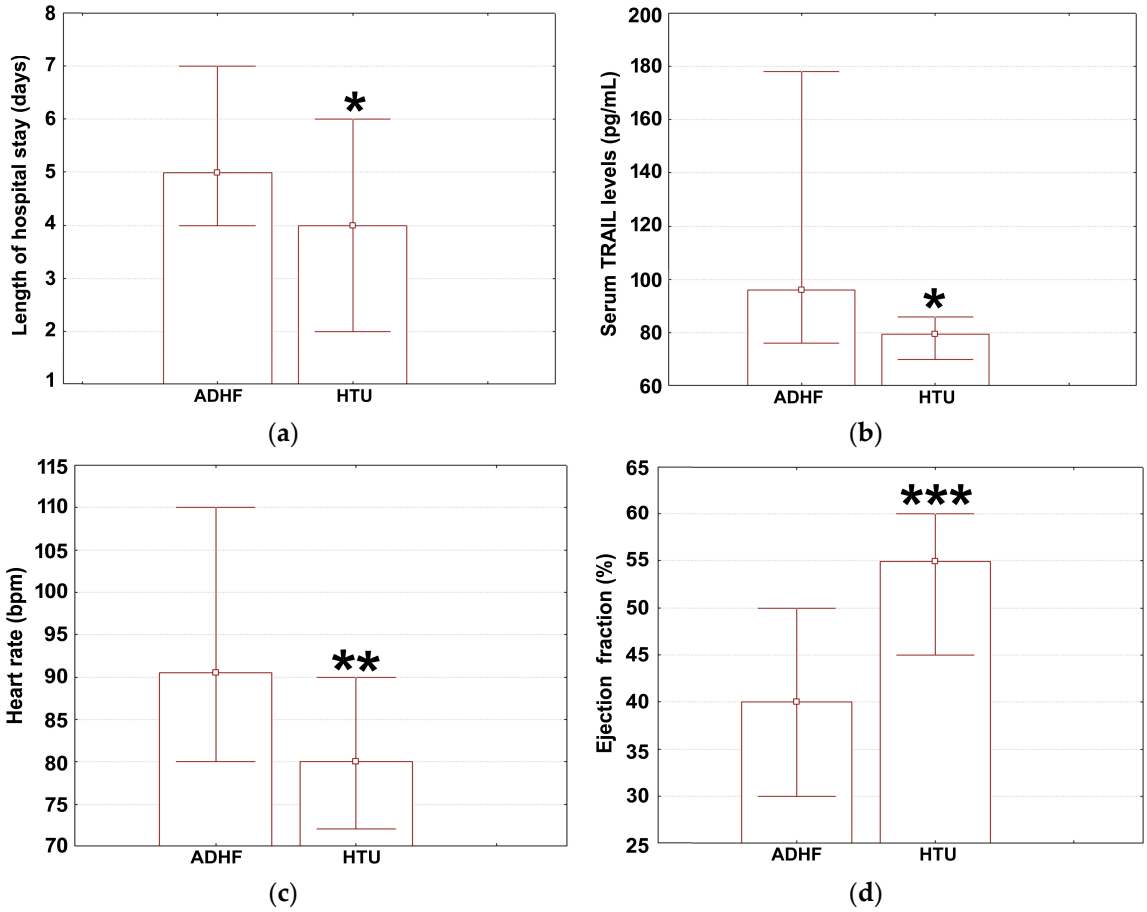


Figure 1. The measured values for (**a**) length of hospital stay, (**b**) TRAIL levels, (**c**) heart rate, and (**d**) ejection fraction in patients hospitalized with hypertensive urgency (HTU) or episodes of acute decompensation of HF (ADHF). Data are given as medians (boxes) with lower and upper quartiles (error bars). Marked boxes (*) denote significant differences compared to patients hospitalized with ADHF (Mann–Whitney U test, ***— $p < 0.001$, **—$p < 0.01$, *—$p < 0.05$).

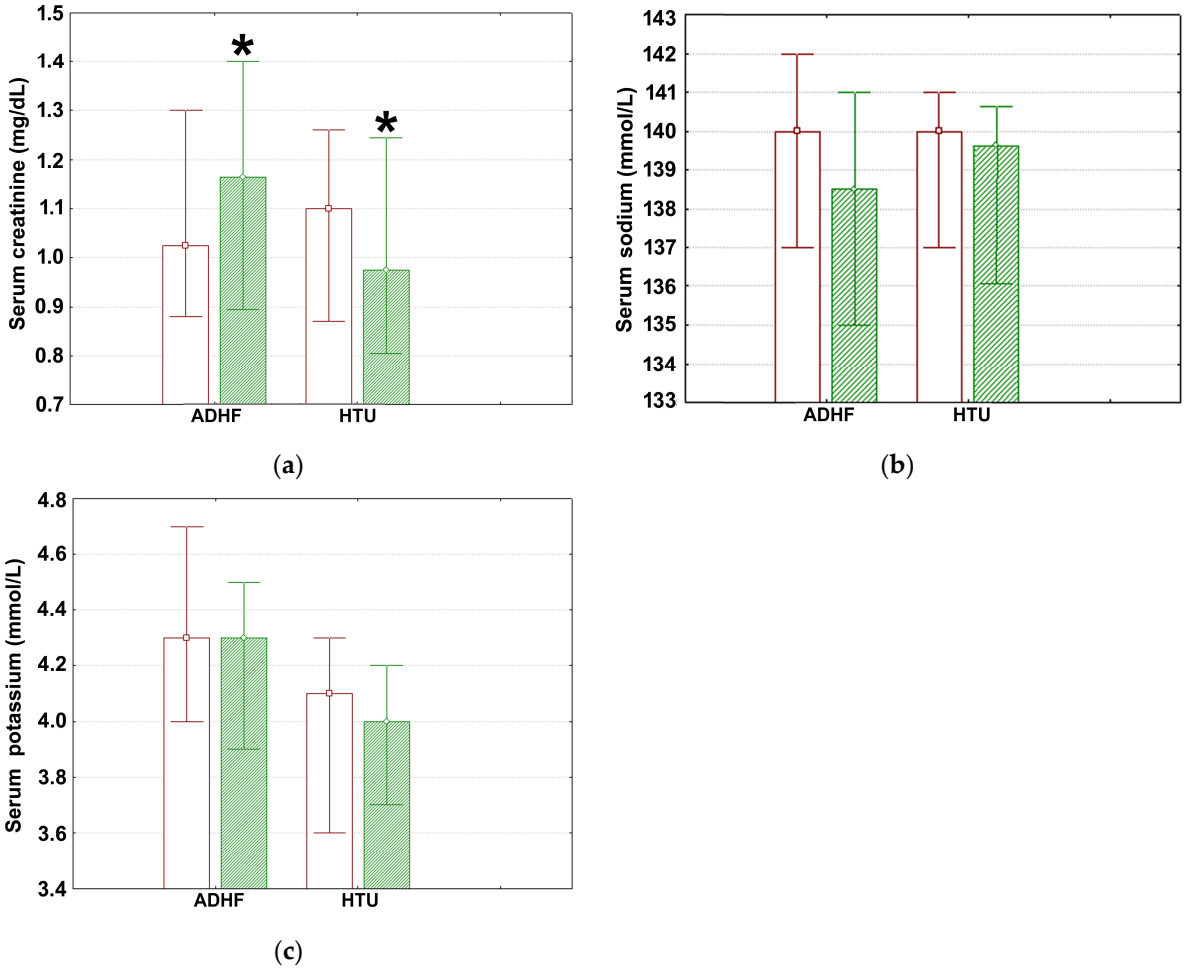


Figure 2. The measured values for (**a**) serum creatinine, (**b**) serum sodium, and (**c**) serum potassium. Data are given as median (box) with lower and upper quartiles (error bars), and measurements were made at both admission (brown box) and discharge (green tint). Marked boxes (*) indicate significant differences at discharge compared to the time of admission (Wilcoxon signed-rank test, ***—$p < 0.001$, **—$p < 0.01$, *—$p < 0.05$).

3.2. Variables Associated with TRAIL Levels

In patients hospitalized for ADHF, TRAIL showed strong positive correlations with ADMA (r = 0.53, $p = 0.015$) and CRP (r = 0.56, $p = 0.010$). It also revealed a moderately positive association with serum potassium at admission (r = 0.42, $p = 0.022$). In patients hospitalized with HTU, TRAIL correlated (moderately) with ADMA again (r = 0.47, $p = 0.019$) and showed a negative moderate association with RDW-SD (r = —0.49, $p = 0.017$). No other significant relationships were seen between ADMA and the other analyzed variables, irrespective of the stratum analyzed ($p \geq 0.098$).

4. Discussion

Although several recent studies have linked TRAIL and its receptors to a variety of cardiovascular diseases, the understanding of their role in the heart is still in its early stages [13,19]. The pioneering data from our study provide the first critical insights into the dynamics of serum TRAIL across different stages of the CVD continuum. Importantly, this study systematically measured TRAIL (and other health indicators) in a uniform cohort of patients at a single facility. This controlled and reliable framework for data accuracy is critical for differentiating between SAH and HF, thereby contributing to a better understanding of role of apoptosis along the CVD continuum. Notably, our findings showed significantly higher TRAIL concentrations during ADHF than in HTU, providing evidence that serum

TRAIL increases as CVD progresses. This is consistent with literature data, although these findings derive from different cohorts of patients and clinical settings [16–18,36,37].

The role of elevated TRAIL in HF is still under debate; however, it is hypothesized to serve as a compensatory mechanism. Thus, elevated serum TRAIL appears to be protective in both preserved EF and reduced EF, highlighting its potential as a beneficial biomarker in HF management [16,17]. In contrast, low levels are associated with an increased risk of rehospitalization and mortality among HF patients over a five-year follow-up period [18,36]. On the other hand, reduced plasma TRAIL concentrations measured 20 weeks prior to gestation have been associated with an elevated risk of developing hypertensive disorders during pregnancy [37]. Given these observations, the role of TRAIL in CVD may derive from its dual functions in cellular cleanup and as part of the body's adaptive responses to ongoing heart and vascular stress [19].

The effective matching methodology; the homogeneity of the study population; and the common prevalence of certain risk factors and comorbidities, such as diabetes and smoking, among patients with heart-related issues may account for the lack of significant inter-group differences in sociodemographic and most clinical characteristics. However, the significant differences in the incidence of renal dysfunction underscores its potential importance in distinguishing between these ADHF and HTU patients.

Shorter hospital stays with HTU may originate from different disease pathophysiology, treatment requirements, and patient management strategies. SAH is a less severe condition than HF, although it can lead to HF development over time [28]. In addition, HTU is associated with fewer complications and can be rapidly controlled with antihypertensive medications, leading to quicker stabilization and discharge [28,38]

The significantly elevated HR and significantly lower EF seen in ADHF (versus HTU) are in line with clinical data [28,39,40]. Associated with altered cardiac output and increased sympathetic activation, HF often prompts compensatory mechanisms such as elevated HR to maintain perfusion to vital organs [39]. Reduced EF implies perturbed contractile function of the heart muscle [40]. As a result, the weakened heart in HF struggles to pump blood efficiently through the body, which attempts to compensate by increasing HR to maintain circulation and overcome the reduced cardiac output.

Elevated SBP in these acute cardiac conditions reflects the increase in systemic vascular resistance derived from the activation of the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system (SNS) in response to neurohormonal stimuli [41]. These mechanisms are particularly pronounced during acute cardiovascular events due to the body's attempt to maintain adequate perfusion despite failing cardiac function or acute stress [41]. Nonetheless, it is worth noting that elevated SBP at hospital admission is associated with better clinical outcomes for both ADHF and HTU [42,43].

RDW-SD and RDW-CV were significantly higher during ADHF than during HTU. Both SAH and HF can alter the heart's ability to pump blood, disrupting erythropoiesis and red blood cell survival due to increased systemic inflammation and oxidative stress [44–46]. However, SAH is associated with less severe systemic inflammation and oxidative stress compared to HF [44–46]. This can explain—at least partly—the significantly higher RDW size variability observed in ADHF. We also infer that the presence of multiple comorbidities (e.g., diabetes, obesity) in HF patients contributes to higher HbA1c [47,48]. However, we cannot exclude the notion that other factors, like the long-term use of certain drugs with effects on glucose metabolism (e.g., loop diuretics, statins) in HF, might have contributed to these outcomes [49].

Significant elevation of serum creatinine at discharge vs. admission in ADHF is indicative of ongoing renal impairment. These changes may stem from renal hypoperfusion, aggressive diuretic therapy during hospitalization, neurohormonal activation, or cardiorenal syndrome [50]. In contrast, decreased creatinine at discharge in hypertensive subjects suggests reversible renal strain and improved renal perfusion post-discharge. Nonetheless, hyperuricemia observed during both types of acute cardiac events indicates kidney dys-

function in all patients [51]. The decline in kidney function was more evident in ADHF patients, as suggested by the significantly higher serum urea at admission [52].

Although typically elevated in HF compared to SAH [53], tryglicerides are lower in certain situations, such as cachexic HF patients. These subjects require complex medical management due to associated progressive muscle wasting, weight loss, and functional impairments [54]. Accompanying these changes are significant declines in serum hemoglobin and lymphocytes [55] and increased variance in red blood cell size (as described above). In older people with HF, anemia is mainly caused by decreased red blood cell production or chronic blood loss, but may also be linked to iron or other nutritional deficits [55]. Furthermore, ALC decrease may reflect inflammatory responses or immunosuppression associated with the underlying pathophysiology of HF [56]. Overall, these data indicate that ADHF patients display worse cardiac, hematologic, and renal profiles, with longer hospital stays and cachexic phenotype.

With respect to correlational analysis, the TRAIL–ADMA association emerged as a thread linking apoptosis, endothelial dysfunction, and the CVD continuum. More specifically, the significant positive associations between these variables during both HTU and ADHF indicate an intertwining pathway between endothelial dysfunction and inflammation/apoptosis processes. Indeed, inflammatory mediators (e.g., cytokines, oxidized lipoproteins) can activate pathways like NF-κB, promoting endothelial dysfunction [57]. Moreover, pathways related to Wnt signaling and PPAR-gamma are essential for connecting endothelial dysfunction to the CVD continuum [58].

In ADHF, TRAIL also displayed strong positive correlations with CRP and serum potassium at admission. The former relationship may reflect the body's attempt to manage damaged/dysfunctional cells via apoptosis exacerbated by the inflammatory milieu specific to ADHF [59]. The second association supports a complex interplay between apoptosis, inflammation, and electrolyte balance in HF [19]. For example, elevated TRAIL may disrupt cell membrane in cardiac cells via apoptosis, raising serum potassium levels [60]. Hyperkalemia may also reflect the effects of drugs such as angiotensin-converting enzyme *(ACE) inhibitors,* angiotensin-receptor blockers (ARBs), or potassium-sparing diuretics [60].

Elevated RDW is an inflammatory biomarker often associated with poor prognosis and adverse cardiovascular outcomes [61,62]. In contrast, TRAIL appears to be protective as cardiovascular diseases progress along the continuum [16–18]. The reverse association seen here between these variables hints at the potential beneficial effect of elevated TRAIL in managing HTU. The mechanism behind this relationship is yet to be understood, but it likely involves a combination of its anti-inflammatory effects, induction of apoptosis in dysfunctional cells, improvement in vascular health, and regulation of erythropoiesis [13,19] rather than the effect of a single factor.

Overall, these associations support that apoptosis is an important player in CVD progression. These data also indicate that endothelial dysfunction is a critical driver of apoptosis during the progression from SAH to HF. In the early phases of the CVD continuum, like SAH, apoptosis also appears to be related to altered erythropoiesis. In contrast, in advanced phases, like HF, perturbed apoptosis is related to increasing inflammation and electrolyte imbalance. These patterns are in line with clinical evidence [8,9,16–18,57,61–63].

Although the present study is subject to several methodological limitations, most of them are routinely encountered in pilot, exploratory investigations [64]. One such drawback is the single-site design. The results obtained might therefore not be applicable to broader populations with different demographic/clinical characteristics [64]. However, this design provided us with homogeneity in patient selection/management and the data collection process. Our investigation also focused on acute episodes across different phases of the CVD spectrum. Although this approach may not offer a precise overview of TRAIL's long-term dynamics and outcomes, it is not inherently a weakness. In fact, acute episodes represent critical moments where biomarkers like TRAIL could offer immediate clinical insights essential for acute patient management. These initial short-term data provide valuable preliminary insights, including cellular stress, inflammatory responses, and other

acute changes, that can inform the design of longer-term studies [29,65]. Moreover, another caveat is the relatively small sample size (45 patients per each group). This can decrease the statistical power while also limiting the robustness of subgroup analyses [23,29,66,67]. While a small sample size limits generalizability, it offers certain advantages, such as cost-effectiveness, faster patient turnaround, and focused data collection and analysis [29,68]. As a result, similar sample sizes are commonly used in pilot clinical investigation [29,31].

These limitations notwithstanding, this work offers valuable insights into the interplay between apoptosis and cardiovascular disease. TRAIL is highly relevant in the context of apoptosis, particularly within the CVD spectrum [22]; hence, our results advance the current understanding of how apoptosis contributes to the progression from SAH to HF. Evaluating a comprehensive biomarker panel is another strong point of the present investigation. This approach offers a holistic view of the disease process, allowing for a more nuanced and accurate understanding of CVD. Although the present findings should be interpreted with caution, this protein has clear potential as a biomarker for monitoring progression along the CVD continuum. Thus, elevated TRAIL, as observed in ADHF versus HTU, may indicate an increase in cardiovascular diseases' severity. Notably, we used a mixed-methods design, which combined longitudinal measurements for key renal variables and cross-sectional data for the other parameters [29,31,69]. This fusion gives a detailed picture of CVD progression and the dynamics of the underlying renal component. Overall, these contributions significantly expand the current status of knowledge on cardiovascular disease pathophysiology, with potential implications for their diagnosis, prognosis, and treatment.

5. Conclusions

This exploratory pilot study offers the first critical insights into the dynamics of serum TRAIL along the CVD continuum in a controlled and reliable framework. Since the measured values were significantly elevated in ADHF versus HTU, our results suggest that TRAIL increases with the severity of cardiovascular disorders. This progressive rise along the CVD spectrum makes TRAIL an interesting candidate as a biomarker to track the development of circulatory diseases. ADHF individuals displayed longer hospital stays; worse cardiac, hematologic, and renal profiles; and cachexic phenotypes. Correlational analysis indicated that endothelial dysfunction is an important component of the interplay between apoptosis and CVD progression. Moreover, these associations provided evidence for a transition from altered erythropoiesis in early stages of CVD to inflammation and electrolyte imbalance in more advanced stages. Overall, our findings expand the current status of knowledge on the role of apoptosis in cardiovascular conditions, providing a holistic view of disease progression.

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