Original paper

# Relationship between expression of blood circulating lncRNA: LRRC75A-AS1, clinical characteristics and prognosis of chronic heart failure patients

## *Zależność pomiędzy ekspresją krążącego we krwi lncRNA: LRRC75A-AS1 a obrazem klinicznym i rokowaniem chorych z przewleką niewydolnością serca*

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**Key words:** chronic heart failure, lncRNA, LRRC75A-AS1, biomarker.

**Słowa kluczowe:** przewlekła niewydolność serca, lncRNA, LRRC75A-AS1, biomarker.

### Abstract

**Introduction:** A complex interplay of genetics and multiple biological mechanisms contributes not only to chronic heart failure (CHF) progression and an unfavorable prognosis, but also makes biomarker selection difficult. Discovery of novel molecular markers, such as lncRNAs, has provided a new approach to biomarker study, including for CHF.
**Aim of the research:** In this study, we focused on blood circulating LRRC75A-AS1 as a novel prospective biomarker reflecting the clinical image and prognosis of CHF patients.
**Material and methods:** The lncRNA expression was examined in plasma samples of 108 newly diagnosed CHF patients and correlated with clinical outcomes.
**Results:** Low expression of LRRC75A-AS1 was associated with a greater inflammatory response reflected by higher plasma concentrations of C-reactive protein, interleukin-6 and tumor necrosis factor α. Patients with low lncRNA expression had lower serum albumin concentration and they were more frequently classified as NYHA grade III or IV, had PASP ≥ 36 mm Hg and more often demonstrated presence of exertional dyspnea. The Cox regression model selected downexpression of LRRC75A-AS1 as an independent prognostic factor related to poor survival of CHF (HR = 2.17).
**Conclusions:** Blood circulating LRRC75A-AS1 seems to be an attractive biomarker supporting clinical assessment of CHF patients. Expression of the lncRNA reflects the extent of the CHF symptoms and severity of the systemic inflammatory response, which can be useful for selection of patients with an unfavorable disease course and higher risk of death.

### Streszczenie

**Wprowadzenie:** Złożone oddziaływanie pomiędzy czynnikami genetycznymi a ogólnoustrojowymi mechanizmami biologicznymi przyczynia się nie tylko do progresji i niekorzystnego rokowania przewlekłej niewydolności serca (PNS), lecz także utrudnia selekcję biomarkerów dla tej choroby. Odkrycie nowych czynników molekularnych, takich jak lncRNAs, zapewniło nowe podejście do poszukiwania biomarkerów chorób, również dla PNS.
**Cel pracy:** W niniejszej pracy skupiono się na krążącym we krwi obwodowej lncRNA – LRRC75A-AS1 jako nowym, potencjalnym biomarkerze odzwierciedlającym kondycję kliniczną oraz rokowanie chorego z PNS.
**Materiał i metody:** Ekspresję lncRNA oceniono w próbkach osocza pobranych od 108 nowo zdiagnozowanych pacjentów z PNS, a następnie skorelowano z parametrami klinicznymi badanych chorych.
**Wyniki:** Niska ekspresja LRRC75A-AS1 była związana z bardziej nasiloną odpowiedzią zapalną odzwierciedlaną przez wysokie stężenie białka C-reaktywnego, interleukiny 6 i czynnika martwicy nowotworów α w osoczu. Chorzy z niską ekspresją lncRNA mieli niższe stężenie albuminy w surowicy, byli istotnie częściej kwalifikowani do grupy III i IV wg NYHA, stwierdzano u nich PASP ≥ 36 mm Hg oraz częściej cierpieli z powodu duszności wysiłkowej. Analiza przeżycia metodą Coxa wyselekcjonowała niską ekspresję LRRC75A-AS1 jako czynnik związany z niekorzystnym rokowaniem chorych z PNS (HR = 2,17).
**Wnioski:** Krążący we krwi LRRC75A-AS1 wydaje się atrakcyjnym biomarkerem pomocnym do oceny stanu klinicznego chorych na PNS. Ekspresja lncRNA odzwierciedla stopień zaawansowania objawów PNS oraz nasilenie stanu zapalnego w organizmie, co może być użyteczne w selekcji pacjentów z niekorzystnym rokowaniem choroby i większym ryzykiem zgonu.

## Introduction

Chronic heart failure (CHF) is a complex disease, which results in poor quality of life of patients and is considered as a significant cause of morbidity and mortality worldwide [1, 2]. Despite the advances in diagnosis and treatment of the disease, the prevalence of CHF is increasing [3, 4]. Although CHF is a well known clinical condition, it often presents with unspecific clinical symptoms, which delays accurate diagnosis and treatment. Additionally, the complex interplay between genetic factors and multiple systemic mechanisms, which include neurohormonal activation, the inflammatory response, myocyte injury and presence of metabolic comorbidities, contributes not only to the progression and unfavorable prognosis of the disease, but also impedes selection of accurate biomarkers [5, 6].

"Traditional" biomarkers, such as cardiac troponins, natriuretic peptides (NPs) and C-reactive protein (CRP) have a relatively established place in clinical practice; however, due to their restricted specificity for CHF, they remain basically a complementary examination to clinical management of the disease [5, 7, 8]. Among the above-mentioned biomarkers of CHF, analysis of brain natriuretic peptide (BNP) or N-terminal pro–B-type natriuretic peptide (NT-proBNP) appears to be the valid gold standard for CHF management, mainly for the disease prognosis, although they have been studied less thoroughly and likely less accurately than in acute HF [5, 9, 10]. Until today, proposed NP cut-off values to exclude CHF have not been clearly defined. It is probably caused by numerous cardiac and systemic conditions affecting NPs' blood concentration, such as acute coronary syndromes, myocarditis, patient's age, obesity, anemia and many others. Therefore, their diagnostic value in chronic disease might be less accurate than in an acute setting [9, 11]. Investigation of novel biomarkers could supplement the diagnostic value of NPs to improve the understanding of the complex background of CHF and allow the selection of patients with unfavorable outcomes.

A novel group of prospective CHF molecular biomarkers includes non-coding RNAs (ncRNAs). Their promising clinical utility has already been proven for other systemic and malignant diseases [12]. Among ncRNAs, the group of long non-coding RNAs (lncRNAs) is considered as putative masters of epigenetic regulation during heart development, cardiac hypertrophy, fibrosis and development of CHF. Several lncRNAs including LIPCAR, MALAT1, and MHRT were identified as factors modifying cellular pathways by alteration of gene expression, and hence can drive heart metabolism toward cardiac failure [13]. In this study, we focused on blood circulating LRRC75A-AS1 (also named SNHG29) as a novel and prospective biomarker for CHF management allowing selection of patients with an unfavorable clinical image and disease prognosis. According to recent studies, LRRC75A-AS1 may regulate the p53 regulatory network and thus be involved in tumorigenesis by the development of specific cancer phenotypes [14, 15]. Furthermore, LRRC75A-AS1 has also been found to be overexpressed in normal cardiac cells. Moreover, it is potentially involved in the inhibition of vascular calcification by sponging miR-200b; however, LRRC75A-AS has not been investigated in CHF contexts, so far [16].

## Material and methods

### Study group

108 patients (56 women and 52 men; mean age: 73 ±13 years) with newly diagnosed CHF were enrolled in the study group (Table 1). Patients were diagnosed and treated at the Clinic of Cardiology and Internal Medicine, 1st Military Hospital in Lublin, Poland between 2013 and 2015. European Society of Cardiology (ESC) criteria were applied in order to make the CHF diagnosis. They involved clinical screening, echocardiographic evaluation (the following parameters were derived: EF% – ejection fraction of the left ventricle, LAD – left anterior descending artery size; LVEDD and LVESD – left ventricular end-diastolic and end-systolic diameters; PASP – pulmonary artery systolic pressure; RVOT – right ventricular outflow tract diameter and TAPSE – tricuspid annular plane systolic excursion) and laboratory examination (serum albumin, NT-proBNP, hemoglobin, CRP). For the study purposes, additional inflammatory markers were tested – serum concentrations of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). Extent of the disease was assessed by the New York Heart Association (NYHA) functional classification (grade I–IV according to the disease severity). The following inclusion criteria for patients' recruitment were defined: 1) signed informed consent to participate in the study, 2) newly diagnosed CHF, 3) Polish adult patients. The exclusion criteria were as follows: 1) recent coronary artery bypass grafting (within last 6 months), 2) acute coronary syndrome, 3) thyroid syndrome; 4) presence of implanted cardioverter defibrillator. The study protocol was approved by the local ethics committee in Medical University in Lublin, Poland (no. of consent: KE-0254/64/2017).

### Molecular testing

5 ml of the whole blood samples were collected from the each study participant. Immediately after blood sampling, specimens were centrifuged for 10 min at 1000×g in order to separate plasma. Afterwards, plasma samples were collected, divided into smaller portions and stored at –80°C until the RNA extraction. A fraction of the total RNA (including lncRNAs) was isolated from 200 µl of plasma using the miRNeasy Serum/Plasma Kit (Qiagen, Germany) according to the manufacturer's protocol. Purified

**Table 1.** Characteristics of the studied CHF patients ($n$ = 108)

| Factor | | Results |
|---|---|---|
| Gender | Male | 52 (48.1%) |
| | Female | 56 (51.9%) |
| Age (mean ± SD) [years] | | 73 ±13 |
| Smoking status | Smoker | 41 (38%) |
| | Non-smoker | 67 (62%) |
| Laboratory examination | Albumin [g/dl] | 3.43 ±0.61 |
| | NT-proBNP [pg/ml] | 2857 (1339–5072) |
| | Hemoglobin [g/dl] | 13.0 ±2.1 |
| | CRP [mg/l] | 4.80 (2.0–19.1) |
| | IL-6 [pg/ml] | 6.22 (1.84–15.73) |
| | TNF-α [pg/ml] | 3.88 (3.15–5.61) |
| NYHA | I | 20 (18.5%) |
| | II | 34 (31.5%) |
| | III | 33 (30.6%) |
| | IV | 21 (19.4%) |
| Echocardiography | EF% | 40 ±13 |
| | PASP [mm Hg] | 41 ±13 |
| | Male – LVEDD [mm] | 57 ±12 |
| | Female – LVEDD [mm] | 56 ±20 |
| | Male – LVESD [mm] | 46 ±12 |
| | Female – LVESD [mm] | 41 ±9 |
| | TAPSE [mm] | 21 ±11 |
| | RVOT [mm] | 35 ±6 |
| | LAD [mm] | 45 ±6 |
| Dyspnea | At rest | 39 (36.1%) |
| | Exertional | 96 (88.9%) |
| | Nocturnal | 36 (33.3%) |
| Comorbidities | Hypertension | 63 (58.3%) |
| | Diabetes mellitus | 38 (35.2%) |
| | Renal failure | 32 (29.6%) |

*CRP – C-reactive protein, EF% – ejection fraction, LAD – left anterior descending artery size, LVEDD and LVESD – left ventricular end-diastolic and end-systolic diameters, NYHA – New York Heart Association, NT-proBNP – N-terminal pro–B-type natriuretic peptide, PASP – pulmonary artery systolic pressure, RVOT – right ventricular outflow tract diameter, TAPSE – tricuspid annular plane systolic excursion.*

RNA was reverse transcribed into the complementary DNA (cDNA) sequences by the iScript cDNA Synthesis Kit (Bio-Rad, USA). Amplification of the target lncRNA – LRRC75A-AS1 – was carried out in the StepOnePlus qPCR device (Applied Biosystems, USA) using specific TaqMan probes supplied by the manufacturer (TaqMan probe ID: Hs00415106_m1, Catalog #: 4331182) and TaqMan Fast Advanced Master Mix (Thermo Fisher Scientific, USA) according to the kit protocol. Each sample was analyzed in triplicate. The level of LRRC75A-AS1 expression was normalized to the GAPDH expression (endogenous control) using $2^{-\Delta Ct}$ and $2^{-\Delta\Delta Ct}$ methods.

### Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the Medical University in Lublin, Poland (no. of consent: KE-0254/64/2017).

### Statistical analysis

MedCalc v.15.8 (MedCalc, Belgium) statistical computer software was applied for all steps of the analysis and generation of graphs. The D'Agostino-Pearson test was used to check data distribution. In the case of a lack of a normal data distribution, non-parametric tests were used, while for a normal data distribution parametric tests were applied. Differences in the value of studied parameters were compared between groups of patients using either the Mann-Whitney *U* test or Student's *t*-test – the data were presented as the median (interquartile range) or the mean ± standard deviation (SD). Spearman's rank correlation was applied to check the relationship between lncRNA expression and values of the examined parameters. Multiple regression analysis was used for selection of NYHA grade predictors. For the survival analysis, both the following tests were used: univariate Kaplan-Meier estimator and Cox proportional-hazard analysis. The results were considered as statistically significant if *p*-values were below 0.05 ($p < 0.05$).

## Results

In the retrospective study, the complete data were available for 108 patients. The study included the following stages: 1) Enrollment of patients with newly diagnosed CHF between 2015 and 2018. Within this time period we collected both the clinical data of patients and blood samples for further molecular testing. 2) From the date of qualification to the study protocol all patients were followed up for 96 months. 3) In 2023 the follow-up period was completed for all enrolled individuals. 4) In 2023, we performed molecular testing and correlated expression of LRRC75A-AS1 with clinical data of the studied patients. The study protocol is presented schematically in Figure 1. Median expression of LRRC75A-AS1 in the study group was 0.011 (0.004–0.031). Expression of the lncRNA over the median value was considered as high, whereas its low expression was considered for values below the median score. High expression of the lncRNA was detected in 26/108 (24.1%) patients, whereas low expression was recorded for 82/108 (75.9%) individuals. First, the values of studied parameters were compared between groups of patients depending on the lncRNA expression level (Table 2). The group of patients with low expression of LRRC75A-AS1 had a significantly lower mean concentration of serum albumin (mean: 3.36 ±0.62 g/dl vs. 3.64 l0.53 g/dl; $p = 0.038$) as well as a higher median serum concentration of CRP (median: 11.64 mg/l vs. 3.22 mg/l; $p = 0.002$), IL-6 (median: 9.90 pg/ml vs. 2.64 pg/ml; $p = 0.021$), TNF-α (median: 4.23 pg/ml vs. 3.49 pg/ml; $p = 0.044$) and NT-proBNP (median: 3255 pg/ml vs. 1687 pg/ml; $p = 0.005$) compared to CHF patients classified in the high LRRC75A-AS1 expression group. Moreover, they were more frequently classified as NYHA grade III or IV (47/82; 57.3%; $p = 0.012$), had PASP ≥ 36 mm Hg (55/82; 67.1%; $p = 0.012$) and more often demonstrated presence of exertional dyspnea (77/82; 93.9%; $p = 0.008$).

Statistically significant negative correlations between expression of the lncRNA and NT-proBNP concentrations (rho = –0.352; 95% CI: –0.521–0.064; $p = 0.009$) as well as lncRNA and NYHA classification (rho = –0.217; 95% CI: –0.391–0.028; $p = 0.025$) were found (Figures 2 A, B). Using the multiple regression model, the independent predictors of the NYHA grade were selected. The following independent predictors of poorer NYHA classification (III or IV) were selected: increase in CRP concentration ($p = 0.041$), presence of the both nocturnal ($p < 0.001$) and rest dyspnea ($p = 0.020$), decrease in EF% ($p = 0.015$) and presence of low lncRNA expression ($p = 0.018$); see Table 3.

During the 96 months of the follow-up 61/108 (56.5%) patients died. The death ratio was as follows: 34.7% (9/26 patients) in the group with high lncRNA expression and 64.4% (52/82 patients) in the group with low lncRNA expression ($p = 0.013$). Kaplan-Meier estimator analysis considered low expression of LRRC75A-AS1 as an unfavorable factor related to short overall survival in CHF patients. Patients with the low lncRNA expression had about 2.5-fold higher risk (HR = 2.51; 95% CI: 1.45–4.33; $p = 0.006$) of death compared to individuals with high expression of LRRC75A-AS1 (median overall survival: 80 months vs. 26 months) (Figure 3).

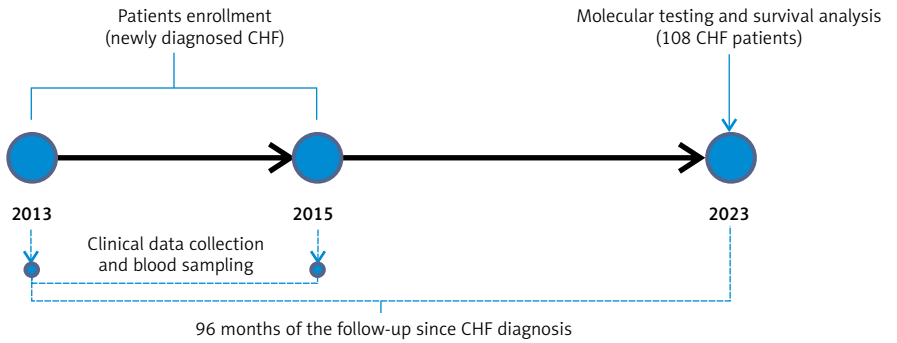


**Figure 1**. Research protocol and stages of the conducted study

**Table 2.** Differences in values of the examined parameters depending on level of LRRC75A-AS1 expression

| Factor | High LRRC75A-AS1 expression ($n$ = 26) | Low LRRC75A-AS1 expression ($n$ = 82) | $P$-value |
|---|---|---|---|
| Albumin [g/dl] | 3.64 ±0.53 | 3.36 ±0.62 | 0.038 |
| NT-proBNP [pg/ml] | 1687 (934–2913) | 3255 (1664–5690) | 0.005 |
| Hemoglobin [g/dl] | 13.3 ±2.2 | 12.9 ±2.1 | 0.457 |
| CRP [mg/l] | 3.22 (1.5–17.2) | 11.64 (2.0–19.9) | 0.002 |
| IL-6 [pg/ml] | 2.64 (1.50–5.60) | 9.90 (1.97–20.38) | 0.021 |
| TNF-α [pg/ml] | 3.49 (2.72–3.81) | 4.23 (3.41–5.65) | 0.044 |
| NYHA I + II | 19 (73.1%) | 35 (42.7%) | 0.012 |
| NYHA III + IV | 7 (26.9%) | 47 (57.3%) | |
| EF% | 42 ±12 | 40 ±13 | 0.761 |
| EF% ≤ 40 | 12 (46.2%) | 43 (52.4%) | 0.655 |
| PASP [mm Hg] | 39 ±13 | 41 ±12 | 0.600 |
| PASP ≥ 36 mm Hg | 10 (42.3%) | 55 (67.1%) | 0.012 |
| Male – LVEDD [mm] | 61 ±10 | 57 ±12 | 0.182 |
| Female – LVEDD [mm] | 57 ±13 | 50 ±7 | 0.581 |
| Male – LVESD [mm] | 50 ±12 | 45 ±12 | 0.260 |
| Female – LVESD [mm] | 41 ±9 | 40 ±8 | 0.707 |
| TAPSE [mm] | 18 ±4 | 22 ±2 | 0.302 |
| TAPSE ≤ 14 mm | 6 (23.1%) | 17 (20.7%) | 0.788 |
| RVOT [mm] | 35 ±5 | 35 ±6 | 0.629 |
| LAD [mm] | 45 ±6 | 44 ±7 | 0.872 |
| Dyspnea at rest | 7 (26.9%) | 32 (39%) | 0.350 |
| Exertional dyspnea | 19 (73.1%) | 77 (93.9%) | 0.008 |
| Nocturnal dyspnea | 7 (26.9%) | 29 (35.4%) | 0.482 |
| Hypertension | 15 (57.7%) | 48 (58.5%) | 1.0 |
| Diabetes mellitus | 6 (23.1%) | 32 (39%) | 0.110 |
| Renal failure | 5 (19.2%) | 27 (32.9%) | 0.224 |

*CRP – C-reactive protein, EF% – ejection fraction, LAD – left anterior descending artery size, LVEDD and LVESD – left ventricular end--diastolic and end-systolic diameters, NYHA – New York Heart Association, NT-proBNP – N-terminal pro–B-type natriuretic peptide, PASP – pulmonary artery systolic pressure, RVOT – right ventricular outflow tract diameter, TAPSE – tricuspid annular plane systolic excursion.*

The Cox proportional hazards model selected independent factors related to higher risk of early death in the studied CHF population (Table 4). A high NT-proBNP concentration was considered as the strongest independent factor related to the reduction of CHF survival (HR = 2.74; $p$ = 0.008). Additionally, presence of exertional dyspnea and low expression of the lncRNA were selected as unfavorable factors related to patient's survival (HR = 2.48; $p$ = 0.012 and HR = 2.17; $p$ = 0.021, respectively).

## Discussion

The discovery of molecular markers such as lncRNAs has initiated a new approach to biomarker study, including for CHF. It is postulated that molecular alterations represent disease at the cellular level and can be detectable prior to manifestation of systemic symptoms. Additionally, they offer a non-invasive and cost-effective manner for biomarker identification. However, the number of studies analyzing the role of blood circulating lncRNAs in cardiovascular diseases is still limited.

The first identified blood circulating lncRNA related to HF was LIPCAR. Zhang *et al*. in a study enrolling 246 patients with myocardial infarction found a connection between LIPCAR and increased risk of HF followed by an unfavorable prognosis [17]. Another study conducted by Luo *et al*. confirmed the pu-

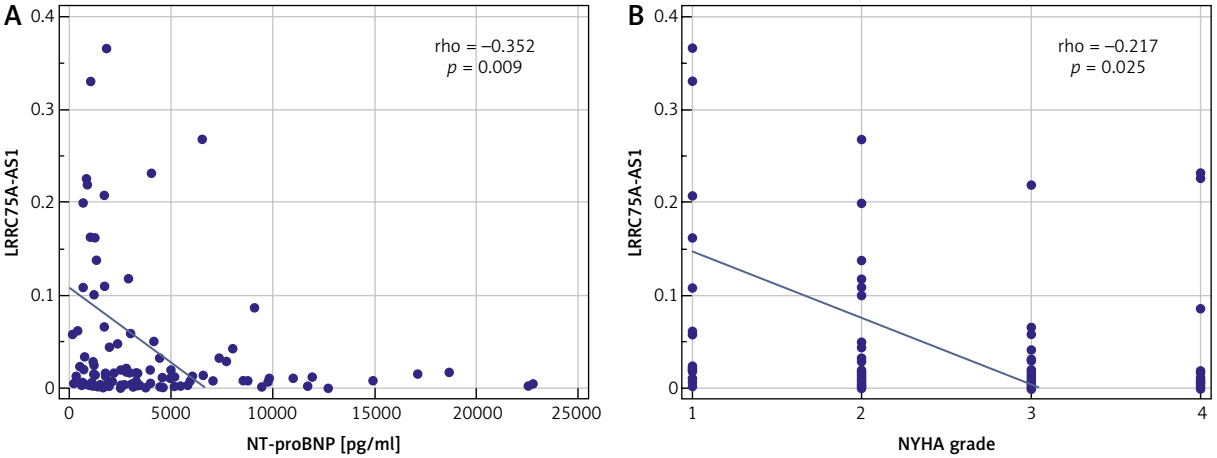


**Figure 2**. Correlation between lncRNA expression and: **A** – serum concentration of NT-proBNP, **B** – NYHA classification

**Table 3.** Significant independent predictors of NYHA III/IV grade selected by multiple regression analysis

| Factor | Coefficient | Std. error | *R* partial | *P*-value |
|---|---|---|---|---|
| CRP | 0.007 | 0.003 | 0.207 | 0.041 |
| Nocturnal dyspnea | 0.889 | 0.203 | 0.409 | < 0.001 |
| Dyspnea at rest | 0.487 | 0.205 | 0.235 | 0.020 |
| EF% | –0.014 | 0.006 | –0.246 | 0.015 |
| LRRC75A-AS1 | –0.380 | 0.157 | –0.240 | 0.018 |

*CRP – C-reactive protein, EF% – ejection fraction.*

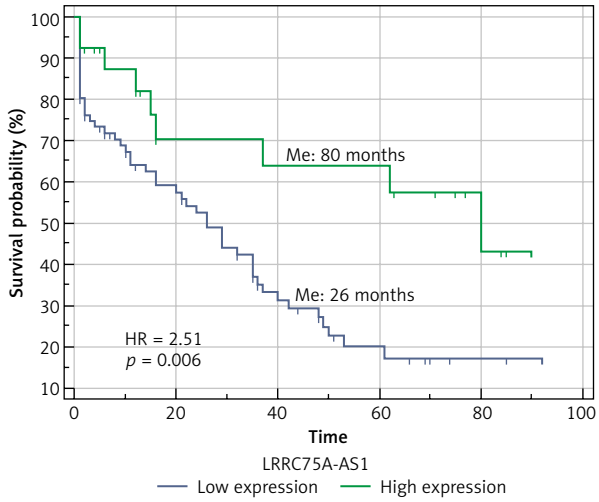


**Figure 3**. Impact of LRRC75A-AS1 expression on survival probability of CHF patients

**Table 4.** Independent factors affecting survival of CHF patients selected by the Cox proportional hazards model

| Factor | HR [95% CI] | *P*-value |
|---|---|---|
| High NT-proBNP concentration | 2.74 [0.98–8.21] | 0.008 |
| Exertional dyspnea | 2.48 [0.90–6.91] | 0.012 |
| Low LRRC75A-AS1 expression | 2.17 [0.34–5.99] | 0.021 |
| Overall model fit: $p < 0.001$ | | |

*NT-proBNP – N-terminal pro-B-type natriuretic peptide.*

tative role of LIPCAR in HF pathogenesis, recording its overexpression in plasma samples of patients with coronary artery disease and concomitant HF [18]. In another study, Deng *et al*. noted low expression of GASL1 in CHF patients compared with healthy individuals. Interestingly, they recorded a negative correlation between plasma expression of GASL1 and plasma concentration of TGF-β.1 Based on the above observation, they assumed the role of the lncRNA in cardiomyocyte apoptosis via modulation of TGF-β1 axis, because low plasma expression of GASL1 was associated with poor survival of CHF individuals [19]. In our study we found the low expression of LRRC75A-AS1 as an unfavorable factor related to about 2.5-fold higher risk (HR = 2.51) of early death in CHF patients within the follow-up period. Although LRRC75A-AS1 has not been investigated in patients with cardiovascular diseases before, its altered expression has been recorded for different human cancers. Similarly to our results, Wang *et al*. found low expression of the lncRNA as a poor prognostic factor for laryn-

geal cancer, and the downregulation of LRRC75A-AS1 corresponded with tumor stage, metastases and differentiation [20]. In addition to the above-mentioned study, LRRC75A-AS1 was remarkably expressed at low levels in colorectal cancer tissues. *In vitro* experiments demonstrated that the inhibition of lncRNA can facilitate colorectal cancer cell proliferation and migration [21]. Recently, Wang *et al.* postulated the involvement of LRRC75A-AS1 in the development of an inflammatory condition related to bovine mastitis. Expression of the lncRNA was found significantly reduced in bovine mammary epithelial cells and mammary tissues under the inflammatory condition. According to the *in vitro* results presented by the authors, LRRC75A-AS1 inhibits activation of the NF-κB signaling pathway as well as Wnt/β-actin signaling, both of which are reported to promote vascular calcification [16, 22]. Interestingly, we have more frequently observed low expression of LRRC75A-AS1 in blood samples of patients demonstrating a higher inflammatory response reflected by plasma concentration of CRP ($p = 0.002$), IL-6 ($p = 0.021$) and TNF-α ($p = 0.044$). Based on the literature findings, we postulate that a decrease in the lncRNA expression can modulate the inflammatory response accompanying CHF via activation of NF-κB signaling and resulting in disease progression and unfavorable outcomes. Patients with low lncRNA expression were more often classified in grade III and IV of NYHA (57.3% patients) and presented exertional dyspnea ($p = 0.008$). Additionally, an inverse correlation with serum concentration of NT-proBNP (rho = –0.352) and NYHA grade (rho = –0.217) was recorded for LRRC75A-AS1. The inflammatory concept seems to be likely confirmed by observations derived from the studies on other lncRNAs. Two downexpressed lncRNAs – ANRIL and HOTAIR – impair the maladaptive myocardial remodeling and increase the expression of inflammatory factors in ischemic myocardial tissue of diabetic rats via modulation of the NF-κB axis [13]. Perhaps, through modulation of the inflammatory condition LRRC75A-AS1 can participate in the disease progression, resulting in an unfavorable clinical picture of CHF patients.

## Conclusions

Analysis of the blood circulating LRRC75A-AS1 seems to be an attractive option for management of CHF patients and a prospective supplementary tool for BNP/NT-proBNP examination. Expression level of the lncRNA reflects the CHF severity and inflammatory condition in the patient's body; thus it allows the selection of patients with an unfavorable prognosis and a worse disease course. The major strength of the present study is the ability to reflect the patient's clinical picture at the time of admission by analysis of the single lncRNA. Additionally, the prognostic value of the blood circulating LRRC75A-AS1 was proven and it allows the selection of patients at high risk of early death. Regarding the weakness of the study, it was performed retrospectively in a relatively small group of patients. The exact mechanism linking LRRC75A-AS1 and CHF needs to be further investigated, and the lncRNA expression requires validation in a much larger group of CHF patients.

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## Conflict of interest

The authors declare no conflict of interest.

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