

## Article

# Lipoprotein(a) Levels in Heart Failure with Reduced and Preserved Ejection Fraction: A Retrospective Analysis

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## Abstract

**Background/Objectives:** While elevated Lp(a) levels are associated with incident heart failure development, the role of Lp(a) in established heart failure with reduced ejection fraction (HFrEF) versus heart failure with preserved ejection fraction (HFpEF) remains unexplored. **Methods:** We conducted a retrospective analysis of 387 heart failure patients from our institutional database (January 2018–June 2024). Patients were categorized as HFrEF ( $n = 201$ ) or HFpEF ( $n = 186$ ) using ICD-10 codes. Categorical variables were compared between heart failure types using the Chi-square test or Fisher's Exact test, and continuous variables were compared using the two-sample  $t$ -test or Wilcoxon rank-sum test, as appropriate. Logistic regression was utilized to assess heart failure type as a function of Lp(a) levels, adjusting for covariates. Spearman correlation assessed relationships between Lp(a) and pro-BNP levels. **Results:** Despite significant demographic and clinical differences between HFrEF and HFpEF patients, Lp(a) concentrations showed no significant variation between groups. Median Lp(a) levels were 60.9 nmol/dL (IQR: 21.9–136.7) in HFrEF versus 45.0 nmol/dL (IQR: 20.1–109.9) in HFpEF ( $p = 0.19$ ). After adjusting for demographic and clinical covariates, Lp(a) showed no association with heart failure subtype (OR: 1.001, 95% CI: 0.99–1.004;  $p = 0.59$ ). **Conclusions:** Lp(a) levels do not differ significantly between HFrEF and HFpEF phenotypes, suggesting possible shared pathophysiological mechanisms rather than phenotype-specific biomarker properties. These preliminary findings may support unified screening and treatment strategies for elevated Lp(a) across heart failure, pending confirmation in larger studies.

**Keywords:** lipoprotein(a); heart failure; molecular pathophysiology; precision medicine; cardiovascular risk; biomarkers



Academic Editors: Alexander E. Berezin and Michael Lichtenauer

Received: 28 June 2025

Revised: 25 July 2025

Accepted: 5 August 2025

Published: 6 August 2025

**Citation:** Agarwal, A.; Sohail, R.; Behuria, S. Lipoprotein(a) Levels in Heart Failure with Reduced and Preserved Ejection Fraction: A Retrospective Analysis. *Hearts* **2025**, *6*, 20. <https://doi.org/10.3390/hearts6030020>

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## 1. Introduction

Lipoprotein(a) [Lp(a)] has emerged as one of the most important genetically determined cardiovascular risk factors, affecting approximately 1.4 billion individuals worldwide [1]. This unique lipoprotein particle consists of a low-density lipoprotein (LDL)-like moiety covalently bound to apolipoprotein(a) [apo(a)], a plasminogen-like protein that confers distinct pathophysiological properties [2]. The genetic determinants of Lp(a) concentration are primarily located in the *LPA* gene, with 70–90% of interindividual variability being heritable, making Lp(a) levels largely resistant to lifestyle modifications [3,4].

### 1.1. Molecular Structure and Pathophysiology of Lipoprotein(a)

The molecular architecture of Lp(a) provides insights into its pathogenic mechanisms. The apo(a) component contains multiple kringle domains, particularly kringle IV type 2 (KIV-2), which exists in variable copy numbers ranging from 3 to >40 repeats [5]. This structural variation inversely correlates with plasma Lp(a) concentrations, with smaller apo(a) isoforms associated with higher Lp(a) levels [6]. The unique structure of Lp(a) confers several pro-atherogenic properties, including enhanced binding to extracellular matrix components, resistance to fibrinolysis due to structural homology with plasminogen, and preferential binding of pro-inflammatory oxidized phospholipids [7,8].

Recent molecular studies have revealed that Lp(a) promotes atherosclerosis through multiple mechanisms: (1) enhanced atherogenesis via preferential accumulation in arterial walls and foam cell formation; (2) increased inflammation through oxidized phospholipid-mediated inflammatory pathways; and (3) impaired fibrinolysis due to competitive inhibition of plasminogen activation [9,10]. These mechanisms establish Lp(a) as an independent and causal risk factor for atherosclerotic cardiovascular disease (ASCVD), as demonstrated by extensive epidemiological and Mendelian randomization studies [11,12].

### 1.2. Lipoprotein(a) and Heart Failure: Emerging Evidence

While the association between Lp(a) and coronary artery disease is well-established, the relationship with heart failure has only recently gained attention. Emerging evidence suggests that elevated Lp(a) levels are associated with incident heart failure development, with studies indicating an increased risk of heart failure per 50 mg/dL increase in Lp(a) levels [13,14]. However, the mechanisms underlying this association remain incompletely understood, particularly regarding the differential roles of Lp(a) in distinct heart failure phenotypes.

The pathophysiology of heart failure comprises heterogeneous syndromes with distinct molecular mechanisms. Heart failure with reduced ejection fraction (HFrEF) is characterized by substantial cardiomyocyte loss, leading to systolic dysfunction and eccentric remodeling [15]. In contrast, heart failure with preserved ejection fraction (HFpEF) involves concentric remodeling with preserved systolic function but impaired diastolic relaxation, often associated with chronic comorbidities such as hypertension, diabetes, and obesity [16,17].

### 1.3. Molecular Differences Between HFrEF and HFpEF

Recent advances in cardiovascular molecular biology have revealed fundamental differences in the pathophysiology of HFrEF and HFpEF. At the cellular level, HFrEF is primarily driven by cardiomyocyte death due to ischemia, leading to compensatory hypertrophy and fibrosis [18]. Key molecular alterations include disrupted calcium handling, impaired mitochondrial function, and activation of maladaptive signaling pathways such as the renin–angiotensin–aldosterone system [19].

HFpEF, conversely, is characterized by a complex interplay of systemic inflammation, endothelial dysfunction, and altered cardiomyocyte stiffness [20]. The molecular mechanisms include: (1) chronic low-grade inflammation triggered by metabolic comorbidities; (2) coronary microvascular dysfunction leading to impaired myocardial perfusion; (3) increased cardiomyocyte passive stiffness due to titin isoform shifts and post-translational modifications; and (4) enhanced interstitial fibrosis [21,22].

### 1.4. Therapeutic Implications and Precision Medicine

The development of Lp(a)-lowering therapies represents a paradigm shift in cardiovascular risk management. Novel antisense oligonucleotides, particularly pelacarsen (TQJ230), have demonstrated the ability to reduce Lp(a) levels by 80–90% in Phase II trials [23,24].

The ongoing Lp(a) HORIZON Phase III trial is evaluating the cardiovascular outcomes of pelacarsen in patients with elevated Lp(a) and established cardiovascular disease [25].

The potential differential effects of Lp(a) in HFrEF versus HFpEF have important implications for precision medicine approaches. If Lp(a) levels or pathophysiological mechanisms differ between heart failure phenotypes, this could justify phenotype-specific screening protocols, risk stratification algorithms, and targeted therapeutic interventions. Conversely, similar Lp(a) levels across heart failure subtypes would support unified treatment strategies, potentially simplifying clinical decision-making.

### 1.5. Study Rationale and Objectives

Despite the growing recognition of Lp(a) as a cardiovascular risk factor, there exists a significant knowledge gap regarding its role in established heart failure, particularly in comparing HFrEF and HFpEF phenotypes. This knowledge gap is particularly relevant given the time-sensitive nature of emerging Lp(a)-lowering therapies and the need for evidence-based treatment guidelines. Therefore, we conducted this retrospective analysis to determine whether Lp(a) concentrations differ between patients with HFrEF and HFpEF, and to explore the potential implications for precision medicine approaches in heart failure management. Our findings could inform future research directions and clinical practice guidelines for Lp(a) management in heart failure patients.

## 2. Materials and Methods

We conducted a retrospective cohort study under approval of the Institutional Review Board (IRB) (Study IRB #24-0582) across Northwell Health institutions. The study was conducted in accordance with the Declaration of Helsinki and all applicable regulatory requirements.

Patients with heart failure were identified using International Classification of Diseases, Tenth Revision (ICD-10) codes from 1 January 2018 to 30 June 2024. Initial screening identified 411 heart failure patients from our institutional database. We categorized patients as having HFrEF (ejection fraction < 40%) or HFpEF (ejection fraction  $\geq$  50%) based on echocardiographic assessments and clinical documentation.

We included patients who were 18 years or older, had a documented diagnosis of HFpEF or HFrEF with available Lp(a) levels. We excluded patients with a diagnosis of both HFrEF and HFpEF ( $n = 12$ ) and those with end-stage kidney disease, liver disease, myocardial infarction, valvular heart disease or cardiomyopathy.

Lp(a) measurements were measured using immunoturbidimetric assay methodology at LabCorp (Laboratory Corporation of America). Results were reported in nmol/L. Fasting was not required prior for Lp(a) measurement, and samples were processed within 24 h of collection. Lp(a) levels were interpreted using our laboratory's reference range with <75 nmol/L considered normal.

Baseline demographic data, clinical characteristics, and laboratory values were extracted from electronic health records. Variables collected included age, sex, race/ethnicity, body mass index, comorbidities such as coronary heart disease, hypertension, diabetes mellitus, atrial fibrillation, dyslipidemia, chronic kidney disease.

Continuous variables are presented as means  $\pm$  standard deviation (SD) for normally distributed data or medians with interquartile ranges (IQR) for non-normally distributed data. Categorical variables are presented as frequencies and proportions. Comparisons between HFrEF and HFpEF groups were performed using chi-square tests or Fisher's exact tests for categorical variables and two-sample *t*-tests or Wilcoxon rank-sum tests for continuous variables, as appropriate. Spearman correlation coefficients were calculated to assess relationships between Lp(a) and pro-BNP levels, both overall and stratified by heart failure subtype. Multivariate logistic regression analysis was performed to determine

the association between Lp(a) levels and heart failure subtype, adjusting for potential confounders including age, sex, race, atrial fibrillation, coronary heart disease, diabetes, and pro-BNP levels.

Statistical significance was defined as  $p < 0.05$ . All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

### 3. Results

#### 3.1. Study Population Characteristics

After applying inclusion and exclusion criteria, 387 patients were included in the final analysis: 201 with HFrEF (52%) and 186 with HFpEF (48%). The overall population had a mean  $\pm$  SD age of  $69 \pm 12.6$  years, with 58% being male ( $n = 225$ ) and 62% being white ( $n = 238$ ).

#### 3.2. Baseline Demographic and Clinical Characteristics

Significant demographic and clinical differences were observed between HFrEF and HFpEF groups (Table 1). Patients with HFrEF were younger ( $65.9 \pm 12.2$  vs.  $72.4 \pm 12.1$  years,  $p < 0.0001$ ) and more likely to be male (74.1% vs. 40.9%,  $p < 0.0001$ ). Coronary heart disease (CHD) was more prevalent in HFrEF patients (83.4% vs. 61.8%,  $p < 0.0001$ ), while hypertension (HTN) and atrial fibrillation (AF) were more common in HFpEF patients (84.8% vs. 74.9%,  $p = 0.02$  and 39.3% vs. 28.6%,  $p = 0.03$ , respectively).

**Table 1.** Baseline Characteristics by Heart Failure Subtype \*.

| Characteristic                       | HFrEF ( $n = 201$ ) | HFpEF ( $n = 186$ ) | $p$ Value |
|--------------------------------------|---------------------|---------------------|-----------|
| Age, years (mean $\pm$ SD)           | $65.9 \pm 12.2$     | $72.4 \pm 12.1$     | $<0.0001$ |
| Male sex, $n$ (%)                    | 149 (74.1)          | 76 (40.9)           | $<0.0001$ |
| White race, $n$ (%)                  | 117 (58.2)          | 121 (65.1)          | 0.43      |
| CHD, $n$ (%)                         | 166 (83.4)          | 110 (61.8)          | $<0.0001$ |
| HTN, $n$ (%)                         | 149 (74.9)          | 151 (84.8)          | 0.02      |
| Diabetes mellitus, $n$ (%)           | 80 (40.2)           | 73 (41.0)           | 0.87      |
| AF, $n$ (%)                          | 57 (28.6)           | 70 (39.3)           | 0.03      |
| Dyslipidemia, $n$ (%)                | 129 (64.8)          | 127 (71.4)          | 0.18      |
| proBNP pg/mL (IQR)                   | 498.5 (217–940)     | 488 (180–1212)      | 0.78      |
| Lipoprotein(a), nmol/dL Median (IQR) | 60.9 (21.9–136.7)   | 45.0 (20.1–109.9)   | 0.19      |

\* 10 patients from our sample were missing data on Diabetes mellitus, HTN, dyslipidemia, CHD and AF.

#### 3.3. Lp(a) Levels and Distribution

The primary finding of our study was that Lp(a) concentrations did not differ significantly between HFrEF and HFpEF groups. Median Lp(a) levels were 60.9 nmol/dL (IQR: 21.9–136.7) in HFrEF patients compared to 45.0 nmol/dL (IQR: 20.1–109.9) in HFpEF patients ( $p = 0.19$ ). The distribution of Lp(a) levels was similar between groups as shown in Table 1.

#### 3.4. Multivariable Analysis and Correlation with Natriuretic Peptides

After adjusting for demographic and clinical covariates in multivariate logistic regression analysis, Lp(a) levels showed no association with heart failure subtype (OR: 1.001, 95% CI: 0.99–1.004;  $p = 0.59$ ). Lp(a) demonstrated no discriminatory value between heart failure phenotypes. Correlation analyses revealed no significant associations between Lp(a) and pro-BNP concentrations ( $r = 0.07$ ,  $p = 0.43$ ). This suggests independent pathophysiological pathways for these biomarkers in heart failure.

## 4. Discussion

### 4.1. Primary Findings

Our study represents a preliminary retrospective analysis comparing Lp(a) levels between HFrEF and HFpEF phenotypes within a single health system. The principal finding is that despite significant demographic, clinical, and pathophysiological differences between these heart failure subtypes, Lp(a) concentrations do not differ significantly between groups. This finding has important implications for our understanding of Lp(a)'s role in heart failure pathophysiology and for the development of precision medicine approaches.

### 4.2. Pathophysiological Implications

#### 4.2.1. Shared Molecular Mechanisms Across HF Subtypes

The absence of significant Lp(a) differences between HFrEF and HFpEF in our cohort may suggest that Lp(a) could contribute to heart failure through shared pathophysiological mechanisms rather than phenotype-specific pathways, though this hypothesis requires confirmation in larger studies.

At the molecular level, Lp(a) contributes to cardiovascular pathology through several mechanisms: (1) enhanced atherogenesis via preferential accumulation in arterial walls and promotion of foam cell formation [26]; (2) increased inflammation through oxidized phospholipid-mediated activation of inflammatory pathways [27]; and (3) impaired fibrinolysis due to structural homology with plasminogen [28]. These mechanisms could contribute to both the atherosclerotic burden underlying HFrEF and the microvascular dysfunction characteristic of HFpEF.

#### 4.2.2. Oxidized Phospholipids and Cardiovascular Inflammation

Recent molecular studies have highlighted the role of oxidized phospholipids (OxPL) bound to Lp(a) in promoting cardiovascular inflammation [29]. OxPL-apo(a) complexes have been shown to activate pro-inflammatory signaling pathways [30]. These inflammatory mechanisms are relevant to both HFrEF and HFpEF pathophysiology, potentially explaining the similar Lp(a) levels observed across heart failure phenotypes.

In HFrEF, chronic inflammation contributes to progressive cardiomyocyte loss and ventricular remodeling [31]. The pro-inflammatory properties of Lp(a) could exacerbate these processes through systemic and local inflammatory effects. In HFpEF, low-grade chronic inflammation is a central pathophysiological mechanism, often triggered by metabolic comorbidities and leading to coronary microvascular dysfunction [32,33]. The inflammatory burden associated with elevated Lp(a) could contribute to the development and progression of HFpEF through these mechanisms.

#### 4.2.3. Endothelial Dysfunction and Microvascular Pathology

Endothelial dysfunction plays a crucial role in both HFrEF and HFpEF, albeit through different mechanisms [34]. In HFrEF, endothelial dysfunction contributes to impaired coronary flow reserve and peripheral vasoconstriction [35]. In HFpEF, coronary microvascular dysfunction is a primary pathophysiological mechanism, leading to impaired myocardial perfusion and increased left ventricular stiffness [20].

Lp(a) has been shown to impair endothelial function through multiple molecular mechanisms: (1) direct cytotoxic effects on endothelial cells through OxPL-mediated oxidative stress [36]; (2) impaired nitric oxide bioavailability due to increased superoxide production [37]; and (3) enhanced expression of adhesion molecules promoting inflammatory cell recruitment [38]. These mechanisms could contribute to endothelial dysfunction in both heart failure phenotypes, supporting the similar Lp(a) levels observed in our study.

### 4.3. Clinical Implications

#### 4.3.1. Unified Screening and Risk Stratification

Our findings raise the possibility that elevated Lp(a) might be considered a common cardiovascular risk enhancer, though this requires validation. If confirmed in larger studies, this could have important implications for clinical practice, as it might support unified screening and risk stratification strategies.

Current guidelines recommend measuring Lp(a) levels once in all adults to guide primary prevention efforts [39]. Our findings suggest that this recommendation should be extended to heart failure patients, with similar risk thresholds applied across HFrEF and HFpEF phenotypes. The absence of phenotype-specific differences argues against the need for subtype-specific screening protocols or risk algorithms.

#### 4.3.2. Therapeutic Implications for Lp(a)-Lowering Therapies

The development of Lp(a)-lowering therapies represents one of the most promising advances in cardiovascular medicine. Several novel agents are currently in clinical development, including antisense oligonucleotides (pelacarsen), small interfering RNAs (olpasiran, zerlasiran, lepodisiran), and assembly inhibitors (muvalaplin) [40,41].

Pelacarsen (TQJ230) is the most advanced Lp(a)-lowering therapy, currently being evaluated in the Phase III Lp(a) HORIZON trial [25]. This antisense oligonucleotide targets the *LPA* gene mRNA, leading to reduced apo(a) synthesis and dramatically lowered Lp(a) levels. Phase II studies demonstrated up to 80% reduction in Lp(a) levels, with 98% of patients achieving target levels < 125 nmol/L [23,24].

If confirmed in larger studies, these findings would suggest that Lp(a)-lowering therapies could be evaluated uniformly across heart failure phenotypes, rather than requiring separate trials for HFrEF and HFpEF. This could accelerate the development and regulatory approval of these therapies, potentially benefiting the estimated 1.4 billion individuals worldwide with elevated Lp(a) levels.

#### 4.3.3. Precision Medicine Considerations

While our findings suggest similar Lp(a) levels across heart failure phenotypes, precision medicine approaches should still consider individual patient characteristics when evaluating Lp(a)-lowering therapies. Factors such as baseline cardiovascular risk, comorbidity burden, and genetic factors influencing Lp(a) levels may still warrant personalized treatment approaches.

Recent genetic studies have identified over 40 variants in the *LPA* gene that influence Lp(a) levels, with some variants having differential effects across ethnic groups [42]. Future research should investigate whether these genetic factors influence the relationship between Lp(a) and heart failure outcomes, potentially identifying subgroups that may benefit most from Lp(a)-lowering therapies.

### 4.4. Molecular Mechanisms of Lp(a) in Heart Failure

Our findings raise important questions about the specific molecular mechanisms through which Lp(a) contributes to heart failure development and progression. While we observed similar Lp(a) levels across heart failure phenotypes, the downstream effects of Lp(a) may differ between HFrEF and HFpEF due to distinct cellular and molecular environments.

Future research should investigate: (1) tissue-specific accumulation of Lp(a) in different heart failure phenotypes; (2) differential oxidized phospholipid profiles between HFrEF and HFpEF; (3) interactions between Lp(a) and phenotype-specific molecular pathways; and (4) temporal changes in Lp(a) levels during heart failure progression.

While Lp(a) levels did not differ between heart failure phenotypes, other Lp(a)-related biomarkers may provide phenotype-specific information. Recent studies have identified oxidized phospholipids on apo(a) and apoB-100 as more specific markers of cardiovascular risk than total Lp(a) levels [43]. Future research should investigate whether these oxidized phospholipid biomarkers differ between HFrEF and HFpEF, potentially providing more precise risk stratification tools.

The molecular complexity of Lp(a) offers multiple potential therapeutic targets beyond simply lowering Lp(a) levels. Strategies targeting specific components of Lp(a), such as oxidized phospholipids or the antifibrinolytic properties of apo(a), may provide more targeted approaches for different heart failure phenotypes [44].

#### 4.5. Limitations

Several limitations should be considered when interpreting our findings. First, this was a retrospective study conducted across the Northwell system, which may limit generalizability to other populations and healthcare systems. Second, the variable timing of Lp(a) measurements relative to heart failure diagnosis represents a significant methodological limitation. Lp(a) levels were obtained at inconsistent time points, which could potentially limit our findings, although Lp(a) levels are generally stable over time due to their genetic determination. Third, we did not assess long-term outcomes such as hospitalization, cardiovascular events, or mortality, which would provide important insights into the prognostic value of Lp(a) in heart failure patients. Fourth, our study did not account for potential confounding factors such as medication effects on Lp(a) levels. Statins, for example, can increase Lp(a) levels by 10–20%, while PCSK9 inhibitors can reduce levels by 20–30% [45]. Future studies should account for these medication effects and consider measuring Lp(a) levels before initiation of lipid-lowering therapies. We did not measure oxidized phospholipids or other Lp(a)-related biomarkers that may provide more specific information about cardiovascular risk. Fifth, our study population was predominantly white, which may limit generalizability to other ethnic groups with different Lp(a) distributions. Additionally, limitations include potential selection bias from unclear indications for Lp(a) testing and lack of HF severity stratification. Our analyses were also limited as 136 participants in the study had missing pro BNP levels.

## 5. Conclusions

This retrospective study provides preliminary evidence suggesting no significant differences in Lp(a) levels across heart failure phenotypes. These initial findings may indicate that Lp(a) could represent a shared cardiovascular risk factor across the HF spectrum, potentially supporting unified screening and treatment strategies rather than phenotype-specific approaches. However, these observations require confirmation in larger, prospective, multi-center studies with standardized Lp(a) measurement protocols and a consistent timeline relative to heart failure diagnosis.

The absence of significant Lp(a) differences between heart failure subtypes has important implications for the development and implementation of Lp(a)-lowering therapies. If confirmed in larger studies, these findings could potentially support evaluating the efficacy of novel Lp(a)-lowering treatments uniformly across heart failure phenotypes, which may facilitate their development and regulatory approval. Larger, prospective studies with standardized Lp(a) measurement protocols are needed to confirm these findings. Future research should focus on investigating the specific molecular mechanisms through which Lp(a) contributes to different heart failure phenotypes, exploring the prognostic value of Lp(a)-related biomarkers, and evaluating the therapeutic potential of Lp(a)-lowering interventions in heart failure patients. These studies will be essential for translating our findings

into improved clinical outcomes for the millions of patients affected by both elevated Lp(a) levels and heart failure worldwide.

**Author Contributions:** Conceptualization, A.A.; methodology, R.S.; software, R.S.; validation, R.S.; formal analysis, R.S.; investigation, A.A.; resources, A.A.; data curation, A.A.; writing—original draft preparation, A.A., R.S. and S.B.; writing—review and editing, A.A.; visualization, S.B.; supervision, S.B.; project administration. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Northwell Health (Study IRB #24-0582, date of the approval: 26 August 2024).

**Informed Consent Statement:** Patient consent was waived due to the retrospective nature of the study and the use of de-identified data.

**Data Availability Statement:** The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

**Conflicts of Interest:** The authors declare no conflicts of interest.

## Abbreviations

The following abbreviations are used in this manuscript:

|       |                                                |
|-------|------------------------------------------------|
| Lp(a) | Lipoprotein(a)                                 |
| HFrEF | Heart Failure with reduced Ejection Fraction   |
| HFpEF | Heart Failure with preserved Ejection Fraction |
| HF    | Heart Failure                                  |

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