Original Article

Testosterone and quality of life in patients with dilated cardiomyopathy

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ABSTRACT
BACKGROUND: Testosterone is an important factor that influences the quality of life in men. The purpose of this study is to evaluate how testosterone level impacts the quality of life in patients with dilated cardiomyopathy.
METHODS: This cross-sectional single-center included 97 male patients with dilated cardiomyopathy, in whom serum testosterone was measured. Health-related quality of life was measured using the translated validated version of the Kansas City Cardiomyopathy Questionnaire (KCCQ-12). We used correlation and multivariable regression to assess the association between KCCQ-12 score, serum testosterone level, and clinical and paraclinical variables.
RESULTS: The mean age of study participants was 58 (range 29–88). The mean LVEF was 25 ±8.61%. The average total serum testosterone level was 3.13 ±2.72 (range 0.19–13.5 ng/ml). The median global KCCQ-12 score was 44.8 (6.2–90.6) representing a poor to fair impairment in quality of life. There was an inverse correlation between the KCCQ-12 score and NYHA class (Pearson coefficient r = 0.847 p<0.001) and a direct correlation with LVEF (r=0.445, p<0.001). Also, the KCCQ-12 score correlated with hemoglobin level (r=0.214, p=0.037) and plasmatic creatinine level (r=-0.296 p= 0.004). In multivariable regression, the independent predictors of health-related quality of life were testosterone, LVEF, and NYHA class.
CONCLUSIONS: The results of this study showed for the first time a significant direct relationship between serum testosterone levels and quality of life in patients with dilated cardiomyopathy.

INTRODUCTION
Heart failure (HF) is the last stage of dilated cardiomyopathy (DCM), the most common type of disease of the heart muscle, occurring mostly in men[1].

Patients with heart failure have a compromised quality of life. Health-related quality of life (HRQoL) has gained increasing importance in being an important outcome indicator[2].

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is the most sensitive specific and responsive health-related quality measure for heart failure being used in numerous studies since its introduction. The KCCQ-12 is the short version, which preserves the validity, reliability, responsiveness, prognostic importance, and interpretability of the original instrument. This self-administered questionnaire quantifies different assessment domains: physical limitation (range 0–100), symptom frequency (range 0–100), quality of life (range 0–100), and social limitation (range 0–100). The summary KCCQ-12 score represents the mean calculated score. A higher score is representative of a better health status[3,4].

In men, testosterone decline with age and is one of the major factors that reduce the quality of life[5]. Low testosterone levels are frequently seen in men with chronic heart failure. Reduced testosterone levels are associated with functional capacity, depression, increased mortality, and more severe heart failure in men[6-8].

Several studies showed that testosterone replacement therapy in patients with heart failure was associated with improved exercise capacity, cardiac function, quality of life, or clinical outcome[9,10].

To date, no study evaluated the direct association between androgen status and HRQoL determinants in symptomatic DCM patients using the KCCQ as a health status measure. This study aimed to evaluate the correlation between serum testosterone levels and HRQoL in patients with DCM.

MATERIALS AND METHODS
We performed a cross-sectional single-center study including 97 patients with DCM who were discharged from the Department of Cardiology of the Emergency County Hospital Craiova, Romania, between September 2020 and May 2021.

Inclusion criteria were the diagnosis of dilated cardiomyopathy: left ventricular ejection fraction <45% and/or left ventricular shortening fraction <25%, measured by transthoracic echocardiography and left ventricular end-diastolic diameter >3.2 cm/m2 (>117% of normal value) and/or left ventricular end-diastolic volume >75 ml/m2, measured by transthoracic echocardiography.

Patients with significant hepatic, renal, hematologic, psychiatric, endocrine disorders, or androgen use were excluded.

The study was approved by the ethics committee of the University of Medicine and Pharmacy under registration number 43/17.06.2020. The study was conducted by the ethical principles of the Declaration of Helsinki and written informed consent was obtained before study enrolment from all patients.

In assessing the HRQoL, the patients were instructed to answer the translated validated version of the Kansas City Cardiomyopathy Questionnaire (KCCQ-12) (license from CV Outcomes Inc), independently with minimal assistance from the investigators.

Blood samples were obtained at hospital discharge each morning, with the patients in a fasted state. Blood chemistry levels: total blood count, creatinine, and glycemia, were performed at the hospital laboratory facility. In addition, blood samples from all participants were collected in tubes containing ethylenediaminetetraacetic acid, centrifugated, frozen, and transported to an associated laboratory. Serum testosterone was measured by Enzyme-Linked Fluorescent Assay. The normal range was between 2.27 to 10.3 ng/ml.

Routine echocardiographic examinations were performed blindly by experienced echocardiographers with standard techniques at the echocardiography core facility[11,12].

Statistical Analysis
The software programs Excel 2021 (Microsoft Corporation, Redmond, WA) and IBM SPSS Statistics 28.0 (IBM, Armonk, NY) were used for analyses. Categorical data are expressed as numbers and percentages; continuous data are presented as mean ± SD. Correlations between the KCCQ-12 score and other parameters were assessed using Person's correlation analysis. We performed multiple regression analyses, allowing for interaction between KCCQ-12 score, serum testosterone level, and other parameters. Two-sided p values ≤ 0.05 were considered statistically significant.

RESULTS
Baseline characteristics are presented in Table 1. The mean age of study participants was 58 (range 28–88). The mean LVEF was 25 ± 8.61%. The mean eGFR was 82.95 ± 40.65 mL/min/1.73 m2. Of the study

population, 36.1% (35 patients) had diabetes mellitus. The average total serum testosterone level of the study population was 3.13 ±2.72 (range 0.19 - 13.5 ng/ml).

Table 1. Baseline Characteristics of Examined Men with DCM

Variables	Men with DCM (n = 97)
Age (years)	58 ± 11.9
BMI, kg/m2	27.26 ± 6.53
Diabetes mellitus, n (%)	35 (36.1)
Rhythm n (%)	
Sinus rhythm	56 (57.7)
Atrial fibrillation	41 (42.3)
LVEF, %	25 ±8.61
NYHA class, n (%)	
I	4 (4.1)
II	26 (26.8)
III	32 (33)
IV	35 (36)
eGFR, mL/min/1.73m2	86.97± 39.63
Hemoglobin level, g/dL	13.86±1.62
Testosterone, ng/ml	3.13 ±2.72

BMI: Body mass index; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; eGFR: estimated glomerular filtration rate.

Health status measured by KCCQ-12

The global HRQoL reflected by the median KCCQ score was 44.8 (6.2–90.6) (Table 2). The symptom frequency assessment domain had the highest median score of 51.1 (0–95.8) points while the lowest median score was 33.9 (0–75) points in the quality-of-life assessment domain (Figure 1).

Table 2. Kansas City Cardiomyopathy Questionnaire results in summary for each of the assessment domains and global KCCQ score

Variable	Results, median (min, max)
Physical limitation (KCCQ12-PL)	43.9 (0–91.5)
Symptom frequency (KCCQ12-SF)	51.1 (0–95.8)
Quality of life (KCCQ12-QL)	33.9 (0–75)
Social limitation (KCCQ12-SL)	50.4 (0–100)
Global KCCQ (KCCQ12)	44.8(6.2–90.6)

Correlation between KCCQ-12 score and other parameters

We correlated the clinical features and parameters of laboratory data, echocardiography, with the score of KCCQ-12. (Table 3)

There was a significant direct relationship between testosterone levels and quality of life (r=0.727, p <0.001) (Figure 2). The KCCQ-12 score presented strong correlations also with NYHA functional class (r=-0.847, p<0.001) and LVEF (r=0.445, p<0.001), and weak but significant correlations with hemoglobin level (r=0.214, p=0.037) and plasmatic creatinine level (r=-0.296
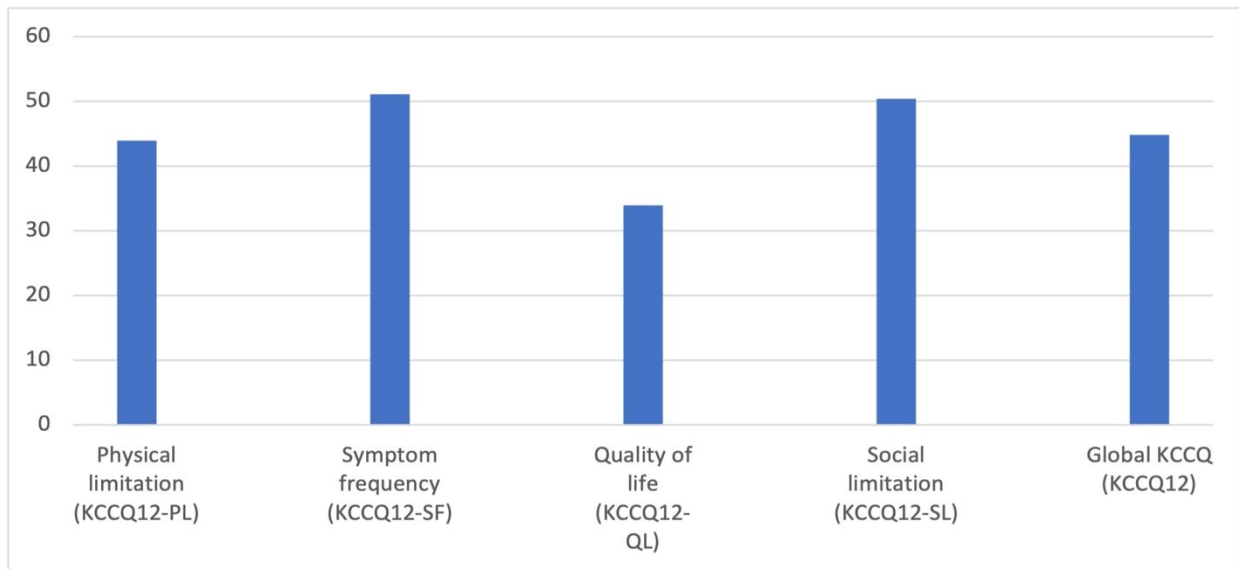

Figure 1. Kansas City Cardiomyopathy Questionnaire results in summary for each of the assessment domains

p=0.004). LVEF correlated especially with the symptom frequency domain (r=0.513, p<0.001).

Table 3. KCCQ12 score correlation analyses with serum testosterone levels and other parameters

Parameters	R	p-value
Testosterone	**0.727**	**<0.001**
Age	-0.124	0.226
BMI	-0.076	0.459
Rhythm	-0.102	0.320
Diabetes mellitus	-0.088	0.394
Serum Creatinine	**-0.296**	**0.004**
Hemoglobin level	**0.214**	**0.037**
LVEF	**0.445**	**<0.001**
NYHA class	**0.847**	**<0.001**

BMI: Body mass index; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

The strongest correlation was between testosterone and the quality-of-life domain (r=0.742, p<0.001).

Correlation between serum testosterone and other parameters
We correlated the clinical features and parameters of laboratory data, echocardiography, with serum testosterone levels. (Table 4)

Beside the direct relationship with KCCQ-12 score, serum testosterone presented strong correlations with NYHA functional class (r=-0.566, p<0.001), with plasmatic creatinine level (r=-0.247 p=0.016) and with age (r=-0.224 p=0.027).

Table 4. Serum testosterone levels correlation analyses with KCCQ score and other parameters

Parameters	R	p-value
KCCQ	0.727	**<0.001**
Age	-0.224	**0.027**
BMI	0.049	0.633
Rhythm	-0.065	0.527
Diabetes mellitus	-0.182	0.075
Serum Creatinine	-0.247	**0.016**
Hemoglobin level	0.118	0.254
LVEF	0.075	0.468
NYHA class	-0.566	**<0.001**

KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

Multiple regression analysis of KCCQ-12 score
Regarding factors that affect the KCCQ-12 score, multiple regression analysis (Table 5) showed that testosterone, LVEF, and NYHA class are
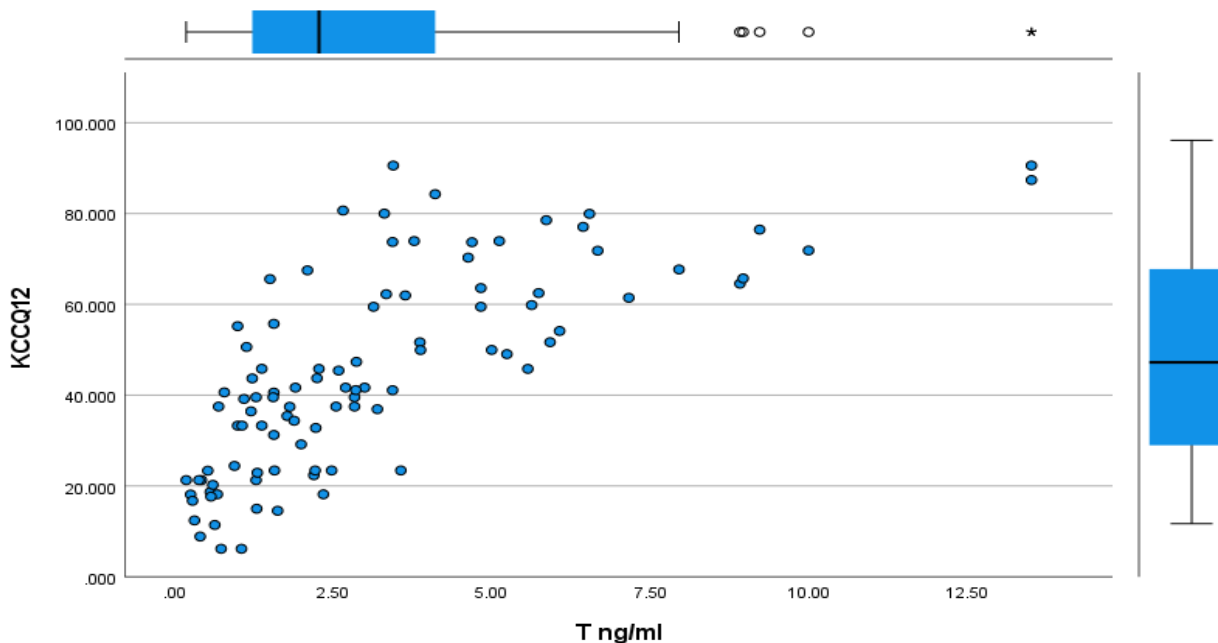

Figure 2. A direct relationship between KCCQ12 and Testosterone

Table 5. Multiple regression analysis (Dependent Variable: KCCQ12)

Model	Standardized Coefficients Beta	p	95.0% Confidence Interval Lower Bound	Upper Bound
(Constant)		<0.001	20.226	69.587
T	**0.443**	**<0.001**	**2.777**	**4.586**
Age	0.025	0.588	-0.120	0.211
Diabetes	-0.023	0.594	-4.807	2.770
Hb	0.064	0.151	-.0314	2.007
LVEF	**0.216**	**<0.001**	**0.308**	**0.804**
NYHA	**-0.489**	**<0.001**	**-14.876**	**-9.287**
Creatinine	-0.073	0.113	-5.955	0.644

T: Testosterone; Hb: hemoglobin; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

Table 6. Multiple regression analysis (Dependent Variable: Testosterone)

Model	Standardized Coefficients Beta	p	95.0% Confidence Interval Lower Bound	Upper Bound
(Constant)		0.393	-2.701	6.802
KCCQ12	**0.989**	**<0.001**	**0.090**	**0.148**
Age	-0.096	0.163	-0.050	0.009
Diabetes	-0.079	0.229	-1.089	0.264
Hb	-0.080	0.233	-0.336	0.083
LVEF	**-0.315**	**<0.001**	**-0.142**	**-0.053**
NYHA	0.139	0.231	-0.269	1.098
Creatinine	0.011	0.878	-0.556	0.649

KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

independent predictors of quality of life in patients with DCM.

Multiple regression analysis of testosterone
Regarding factors that affect testosterone level, after multiple regression analysis (Table 6) only LVEF and KCCQ-12 were independent predictors.

DISCUSSION AND CONCLUSION
The primary treatment goal for patients with heart failure is to alleviate their symptoms and quality of life. Patients with poor quality of life have a worse prognosis and increased severity of heart failure[1].

KCCQ is a well-established instrument to measure the quality of life in this population. It is independently associated with mortality and hospitalizations. and U.S. Food and Drug Administration (FDA) has approved KCCQ as a clinical outcome assessment[13].

NYHA functional classification is the most used health status measure for patients with heart failure. Like other studies, we find a strong correlation between the KCCQ-12 score and NYHA class. More and more studies support the use of KCCQ-12 in routine clinical care, showing that it could have incremental value over the NYHA classification[14,15].

In our study hemoglobin level correlated with quality of life. Anemia is a serious co-morbidity in chronic heart failure patients. Its influence on health-related quality of life in HF patients was reported in other studies[16]. We can speculate that correction of anemia could improve life quality in these patients.

- ***Health-related quality of life is an important outcome indicator in patients with HF***

- ***KCCQ should be used in routine clinical care***

- ***Low testosterone is associated with poor life quality in men with heart failure***

As well as anemia, chronic kidney disease is a predictor of adverse outcomes in heart failure[17].We found a direct association between level of creatinine and life quality. Creatinine level was also correlated with testosterone level. Studies shows that low testosterone is associated with reduced kidney function. This link is multifactorial by dysregulation in the hypothalamic-pituitary-gonadal axis[18]. Kidney disease is prevalent in patients with heart failure being an independent prognostic factor[19].

Although studies didn't show a difference in quality of life between patients with heart failure and preserved ejection fraction and patients with heart failure and reduced ejection fraction[20], LVEF is a powerful predictor of cardiovascular outcomes in heart failure patients. In our cohort, the LVEF was low and was associated with poor quality of life, especially in the domain of symptom frequency. Low LVEF was associated with mortality and hospitalization in patients with heart failure and in a wide range of clinical settings including during noncardiac admissions[21].

Poor health-related quality of life is common in heart failure, but there are little data on HRQoL in HF, and how this is influenced by testosterone. Several small intervention studies had shown the links between low testosterone and impaired exercise capacity in men with HF[8-10]. The present study is the first to report an association between decreased testosterone and poor life quality in men with heart failure. Testosterone deficiency is common in men with heart failure, and studies have shown an association between low testosterone levels and poor cardiovascular outcomes[6]. In our cohort the level of testosterone was low and was associated with a lower KCCQ-12 score, especially in the quality-of-life domain, independently of older age, and cardiac function. Testosterone deficiency is associated with erectile dysfunction, decreased energy, and depression[8], all of these being associated with life quality.

Although there are limited data on testosterone supplementation, more studies show that might be an additional therapy in men with HF, particularly in those with testosterone deficiency[6].

As a limitation, this is a prospective cohort study of a single center with a relatively small number of patients. Also, this study included only inpatients with decompensated DCM and may not be representative of all men with HF. Further studies with a larger and more mixed population are needed.

Conflict of Interest
The authors declare no conflicts of interest.

References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Sep 21;42(36):3599-3726. doi: 10.1093/eurheartj/ehab368.

2. Johansson I, Joseph P, Balasubramanian K, McMurray JJV, Lund LH, Ezekowitz JA et al. Health-Related Quality of Life and Mortality in Heart Failure: The Global Congestive Heart Failure Study of 23 000 Patients From 40 Countries. Circulation. 2021 Jun;143(22):2129-2142. doi: 10.1161/CIRCULATIONAHA.120.050850.

3. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol. 2000

Apr;35(5):1245-55. doi: 10.1016/s0735-1097(00)00531-3

4. Capota R, Militaru S, Ionescu AA, et al. Quality of life status determinants in hypertrophic cardiomyopathy as evaluated by the Kansas City Cardiomyopathy Questionnaire. Health Qual Life Outcomes. 2020 Oct 30;18(1):351. doi: 10.1186/s12955-020-01604-9

5. Moncada I. Testosterone and men's quality of life. Aging Male. 2006 Dec;9(4):189-93. doi: 10.1080/13685530601003180.

6. Diaconu R, Donoiu I, Mirea O, Bălşeanu TA. Testosterone, cardiomyopathies, and heart failure: a narrative review. Asian J Androl. 2021 Jul-Aug;23(4):348-356. doi: 10.4103/aja.aja_80_20

7. Yoshihisa A, Suzuki S, Sato Y, Kanno Y, Abe S, Miyata M, et al. Relation of Testosterone Levels to Mortality in Men with Heart Failure. Am J Cardiol. 2018 Jun 1; 121 (11): 1321-1327. doi: 10.1016/j.amjcard.2018.01.052

8. Bocchi EA, Carvalho VO, Guimaraes GV. Inverse correlation between testosterone and ventricle ejection fraction, hemodynamics and exercise capacity in heart failure patients with erectile dysfunction. Int Braz J Urol. 2008 May-Jun;34(3):302-10; discussion 310-2. doi: 10.1590/s1677-55382008000300007

9. Mirdamadi A, Garakyaraghi M, Pourmoghaddas A, Bahmani A, Mahmoudi H, Gharipour M. Beneficial effects of testosterone therapy on functional capacity, cardiovascular parameters, and quality of life in patients with congestive heart failure. Biomed Res Int. 2014;2014:392432. doi: 10.1155/2014/392432

10. Jankowska EA, Filippatos G, Ponikowska B, Borodulin-Nadzieja L, Anker SD, Banasiak W, et al.. Reduction in circulating testosterone relates to exercise capacity in men with chronic heart failure. J Card Fail. 2009 Jun;15(5):442-50. doi: 10.1016/j.cardfail.2008.12.011

11. Diaconu R, Schaaps N, Afify M, Boor P, Cornelissen A, et al. Apolipoprotein E4 Is Associated with Right Ventricular Dysfunction in Dilated Cardiomyopathy-An Animal and In-Human Comparative Study. Int J Mol Sci. 2021 Sep 7;22(18):9688. doi: 10.3390/ijms22189688

12. Neagoe O, Ciobanu A, Diaconu R, Mirea O, Donoiu I, Militaru C. A rare case of familial restrictive cardiomyopathy, with mutations in MYH7 and ABCC9 genes. Discoveries (Craiova). 2019 Sep 30;7(3):e99. doi: 10.15190/d.2019.12

13. Nassif M, Fine JT, Dolan C, Reaney M, Addepalli P et al. Validation of the Kansas City Cardiomyopathy Questionnaire in Symptomatic Obstructive Hypertrophic Cardiomyopathy. JACC Heart Fail. 2022 Aug;10(8):531-539. doi: 10.1016/j.jchf.2022.03.002

14. Hawwa N, Vest AR, Kumar R, Lahoud R, Young JB, et al. Comparison Between the Kansas City Cardiomyopathy Questionnaire and New York Heart Association in Assessing Functional Capacity and Clinical Outcomes. J Card Fail. 2017 Apr;23(4):280-285. doi: 10.1016/j.cardfail.2016.12.002

15. Greene SJ, Butler J, Spertus JA, et al. Comparison of New York Heart Association class and patient-reported outcomes for heart failure with reduced ejection fraction. JAMA Cardiol. 2021; 6(5):522 doi: 10.1001/jamacardio.2021.0372

16. Kraai IH, Luttik ML, Johansson P, De Jong RM, Van Veldhuisen DJ, et al. Health-related quality of life and anemia in hospitalized patients with heart failure. Int J Cardiol. 2012 Nov 29;161(3):151-5. doi: 10.1016/j.ijcard.2012.05.036

17. Luthi, JC., Flanders, W.D., Burnier, M. et al. Anemia and chronic kidney disease are associated with poor outcomes in heart failure patients. BMC Nephrol 7, 3 (2006). doi: 10.1186/1471-2369-7-3

18. Kurita N, Horie S, Yamazaki S, Otani K, Sekiguchi M, Onishi Y, et al. Low Testosterone Levels and Reduced Kidney Function in Japanese Adult Men: The Locomotive Syndrome and Health Outcome in Aizu Cohort Study. J Am Med Dir Assoc. 2016 Apr 1;17(4):371.e1-6.doi: 10.1016/j.jamda.2016.01.011

19. Vindhyal MR, Khayyat S, Shaaban A, Duran BA, Kallail KJ. Decreased Renal Function is Associated with Heart Failure Readmissions. Cureus. 2018 Aug 9;10(8):e3122. doi: 10.7759/cureus.3122

20. Hoekstra T, Lesman-Leegte I, van Veldhuisen DJ, Sanderman R, Jaarsma T. Quality of life is impaired similarly in heart failure patients with preserved and reduced ejection fraction. Eur J Heart Fail. 2011 Sep;13(9):1013-8. doi: 10.1093/eurjhf/hfr072

21. Curtis JP, Sokol SI, Wang Y, Rathore SS, Ko DT, Jadbabaie F, et al. The association of left ventricular ejection fraction, mortality, and cause of death in stable outpatients with heart failure. J Am Coll Cardiol. 2003 Aug 20;42(4):736-42. doi: 10.1016/s0735-1097(03)00789-7