Clinical Investigations

Correlation of the New York Heart Association Classification and the 6-Minute Walk Distance: A Systematic Review

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ABSTRACT

Background: Functional status assessment is the cornerstone of heart failure management and trials. The New York Heart Association (NYHA) classification and 6-minute walk distance (6MWD) are commonly used tools; however, the correlation between them is not well understood.

Hypothesis: We hypothesised that the relationship between the NYHA classification and 6MWD might vary across studies.

Methods: A systematic literature search was performed to identify all studies reporting both NYHA class and 6MWD. Two reviewers independently assessed study eligibility and extracted data. Thirty-seven studies involving 5678 patients were included.

Results: There was significant heterogeneity across studies in 6MWD within all NYHA classes: I ($n=16$, $Q=934.2$; $P<0.001$), II ($n=25$, $Q=1658.3$; $P<0.001$), III ($n=30$, $Q=1020.1$; $P<0.001$), and IV ($n=6$, $Q=335.5$; $P<0.001$). There was no significant difference in average 6MWD between NYHA I and II (420 m vs 393 m; $P=0.416$). There was a significant difference in average 6MWD between NYHA II and III (393 m vs 321 m; $P=0.014$) and III and IV (321 m vs 224 m; $P=0.027$). This remained significant after adjusting for region of study, age, and sex.

Conclusions: Although there is an inverse correlation between NYHA II–IV and 6MWD, there is significant heterogeneity across studies in 6MWD within each NYHA class and overlap in 6MWD between NYHA I and II. The NYHA classification performs well in more symptomatic patients (NYHA III/IV) but less so in asymptomatic/mildly symptomatic patients (NYHA I/II). Nonetheless, the NYHA classification is an easily applied first-line tool in everyday clinical practice, but its potential subjectivity should be considered when performing comparisons across studies.

Introduction

The New York Heart Association (NYHA) classification system was first developed in 1928 and has since undergone several revisions.[1] The ease of application of this classification based on patients' reported symptoms has resulted in widespread use in many heart failure (HF) studies[2,3] and international guidelines.[4,5] The NYHA classification is often used as inclusion or exclusion criteria for therapy as well as for prognostication and assessment of outcomes.[2–5] Contrary to its extensive use, the actual objectivity of the NYHA is unclear. The NYHA classification is based on patient and physician assessment of cardiac symptoms including dyspnea, angina, and fatigue at different levels of physical activity, and its reliability and validity have been widely debated.[6–8]

Studies have evaluated the usefulness and reliability of more objective measures of HF severity, such as cardiopulmonary exercise testing (CPET) and bicycle and treadmill testing.[9] Although CPET is regarded as the gold standard for assessment of aerobic functional capacity,[10] there are significant financial and logistical costs involved. A viable alternative is the 6-minute walk distance (6MWD), where the distance ambulated on a level surface within 6 minutes is used as a simple and inexpensive yet objective grading of HF severity and prognosis.[11–13] Many studies have shown the objectivity and added prognostic value of the 6MWD in predicting outcomes.[11–13]

To date, there has not been any comprehensive literature review on the correlation between NYHA class and 6MWD. We aimed to assess the correlation between NYHA class

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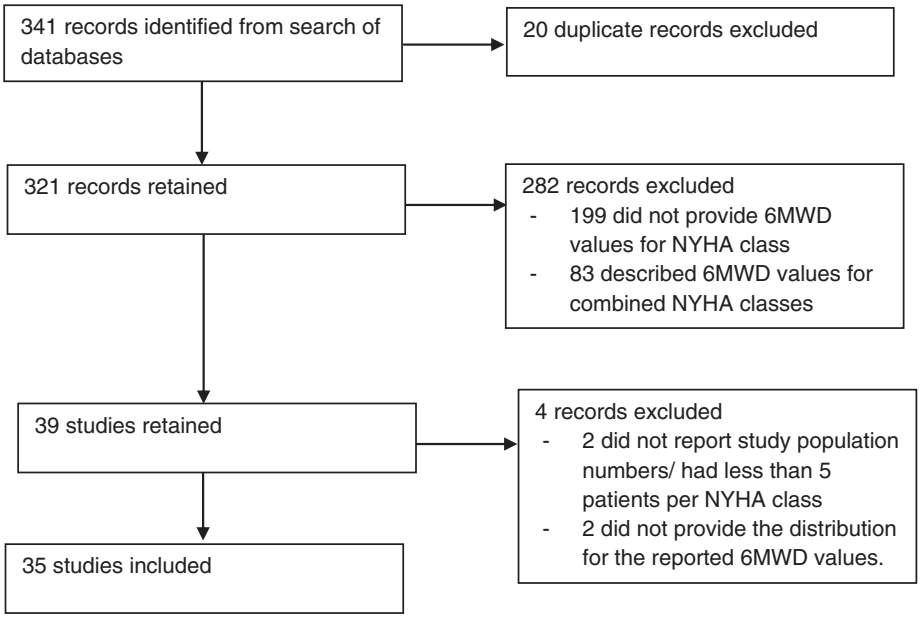

Figure 1. Flowchart of study selection. Abbreviations: 6MWD, 6-minute walk distance; NYHA, New York Heart Association.

and 6MWD by conducting a systematic review of all studies reporting both NYHA class and 6MWD.

Methods

Literature Search Strategy

A comprehensive search of the MEDLINE, Embase, and Cochrane Library databases was performed from January 1980 to Decemebr 2013 by 2 independent reviewers. The search terms used included "heart failure," "congestive cardiac failure," "New York Heart Association," "six minute walk test," and "six minute walk distance." In addition, the references of the included studies and the bibliographies of review articles were searched for additional articles. There was no language restriction. The investigation conformed with the principles outlined in the Declaration of Helsinki. Because the study was based on review of existing literature with no active participation from study subjects, no approval from an ethics committee was required locally.

Inclusion and Exclusion Criteria

Only studies that provided the average 6MWD and its distribution for each individual class of NYHA were included. Studies that did not report the number of patients in each class, or where there were <5 patients in each class, were excluded. Studies that reported average 6MWD for combined NYHA classes (eg, combined class I–II) were also excluded. Figure 1 describes the study selection process.

Data Extraction and Study Characteristics

Two reviewers (F.Y.L., L.L.T.) independently assessed the eligibility of the studies and performed data extraction on a prespecified data-collection form. Discrepancies were resolved by consensus and consultation with a third investigator (J.Y.). Study characteristics collected included the date and type of study; region of study; number, age, and sex of study population; and average 6MWD and its distribution per NYHA class.

Statistical Analysis

For the pooled mean of the 6MWD, we used a random-effects model based on the DerSimonian and Laird method.[14,15] Random-effect models methodology was selected as it was anticipated that systematic differences between studies (heterogeneity) would be likely. A Q statistic and corresponding P value was calculated using χ^2 test to quantify the heterogeneity among combined results. Inconsistency was calculated using an I^2 index to determine the impact of heterogeneity.

For each of the 4 NYHA classes, a separate meta-analysis was performed to estimate the pooled mean of the 6MWD. Forest plots were produced to illustrate mean of 6MWD and its 95% confidence interval (CI). The studies are ordered by the size of the study, from the largest to smallest. In studies where median and interquartile range (IQR) of 6MWD were reported instead of mean and SD, estimation of the mean using IQR was determined within each of the NYHA classes. In these imputations, we assumed the distribution of 6MWD was similar to the normal distribution as the estimated average of 6MWD was close to the reported median.

To identify the association between 6MWD and NYHA, we further undertook study-level meta-regression analysis to assess the effects of NYHA, controlling for region, age, and sex (% of male sex). In this analysis, we compared the mean of the 6MWD for one class of NYHA to the next (adjacent) class, such as I vs II, II vs III, and III vs IV. Average age of each NYHA class was used as a continuous variable. Due to small numbers in the subgroups, region was categorized to 3 groups (North America, Europe, Others) in the meta-regression analysis. The predicted 6MWD with multiple linear model of NYHA class, region, age, and sex was shown

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Table 1. Summary of Included Studies

Study	Country (Region)	Study Type	No. of Patients	Age, years, (SD/Range)	Male Sex, %	LVEF, %, SD (Range)	Data on NYHA Class(es)
Goode et al 2008[7]	UK (Europe)	Case–control	1139	71 (64–77)	—	<40	I, II
Rostagno et al 2003[13]	Italy (Europe)	Cohort	146	64 (10)	—	46	I, II
Alahdab et al 2009[18]	US (North America)	Cohort	198	55.7 (12.9)	63.1	29 (40)	I, II, III, IV
Forman et al 2012[20]	US (North America)	Cohort	2054	59 (51–68)	71.0	≤35	II, III
Zugck et al 2000[21]	Germany (Europe)	Cohort	113	54 (12)	79.646	19	I, II, III
Radke et al 2005[24]	US (North America)	Cohort	17	—	52.9	—	I
Gary et al 2004[25]	US (North America)	RCT	32	—	0	55	II, III
Ingle et al 2008[26]	UK (Europe)	Case–control	186	—	—	—	I, II
Boşnak Guçlu et al 2011[27]	Turkey (Other)	Cohort	34	69 (10)	82	34 (8)	II, III
Karavidas et al 2010[28]	Greece (Europe)	Case–control	18	62 (10)	77.8	<35	II
Jankowska et al 2008[29]	Poland (Europe)	Cohort	10	70 (6)	90	30 (5)	II, III
Ates et al 2013[30]	Turkey (Other)	Cohort	29	64 (7)	52	32 (3)	II
Keast et al 2013[31]	Canada (North America)	RCT	27	62.5 (11.4)	81.5	27 (5)	III
Pepera et al 2012[32]	UK (Europe)	Case–control	10	—	80	46	I
Zaidi et al 2013[33]	US (North America)	Cohort	5	35.5 (25–42)	—	48 (9)	II
Jaski et al 2011[34]	US (North America)	Cohort	39	60.5 (11.4)	87.2	22	III
Leszek et al 2010[35]	Poland (Europe)	Cohort	34	61.5 (9.0)	61.8	57 (12)	II, III
Jehn et al 2009[36]	Germany (Europe)	Cohort	50	60.9 (14.0)	76	39 (16)	I, II, III
Goscinska-Bis et al 2008[37]	Poland (Europe)	RCT	23	64.7 (7.0)	87.0	30 (3)	III
Miller et al 2007[38]	US (North America)	Cohort	25	50.1 (13.1)	—	16 (6)	IV
Freimark et al 2007[39]	Israel (Other)	Case–control	56	—	76.8	—	II
Román et al 2006[40]	Spain (Europe)	Cohort	22	45.4 (19–77)	18.2	—	II
Torre-Amione et al 2005[41]	US (North America)	RCT	37	—	70	22	II
Ince et al 2004[42]	Germany (Europe)	RCT	6	—	100	28 (9)	III
Guimãraes et al 2002[43]	Brazil (South America)	Cohort	12	45 (12)	100	23 (7)	III
Lellamo et al 2010[44]	Italy (Europe)	RCT	32	69 (8)	0	33 (6)	III
Rostagno et al 2000[45]	Italy (Europe)	Cohort	140	45.4 (29–70)	—	35	I, II, III, IV
Rostagno et al 2000[46]	Italy (Europe)	Cohort	33	57.3 (31–72)	—	38	I
Faggiano et al 1997[47]	Italy (Europe)	Cohort	26	56 (11)	92	22 (6)	II, III, IV
Bagur et al 2011[48]	Canada (North America)	Cohort	46	56 (8)	—	53 (15)	I, II, III
Tay et al 2011[49]	UK (Europe)	Cohort	12	80 (10)	17	≥40	II, III
Jehn et al 2010[50]	Switzerland (Europe)	Cohort	97	34 (13)	76	40 (18)	I, II, III
Vrtovec et al 2013[51]	Slovenia (Europe)	RCT	40	61 (10)	85	26 (4)	III
Deuschle et al 2011[52]	Germany (Europe)	Cohort	95	56 (25–80)	—	60 (22–77)	I, II, III, IV
Souza et al 2007[53]	Brazil (South America)	Cohort	38	37 (2)	—	—	I, II, III, IV

Abbreviations: LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RCT, randomized controlled trial; SD, standard deviation; UK, United Kingdom; US, United States.

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in the scatter plot. Stata software version 13 (StataCorp, Ltd., College Station, TX) was used for all analyses.

Results

Out of 321 studies, 35 studies involving 5422 patients met the study criteria and were included. Ten (29%) studies were from North America, 20 (57%) were from Europe, and 5 (14%) were from other regions (eg, South America, Asia). Table 1 describes the characteristics of the included studies. Sixteen studies reported data on NYHA class I, 24 on NYHA class II, 29 on NYHA class III, and 7 on NYHA class IV.

Analysis Within Each New York Heart Association Class

An analysis of the reported 6MWD by NYHA classes showed a pooled estimate of 358 m ($P < 0.0001$; $Q = 5580.1$) and higher 6MWD associated with lower NYHA functional class (Table 2). There was significant heterogeneity between studies seen in each of NYHA classes (all $P < 0.0001$; $Q = 934.2$, 1657.6, 964.0, and 248.4 for NYHA classes I, II, III, and IV, respectively; Table 2 and Figure 2).

Analysis Across New York Heart Association Classes

When adjacent classes of NYHA are compared, the smallest difference between 6MWD was seen in patients with class I and II (420 m vs 393 m) and the largest difference was in patients with classes III and IV (325 m vs 225 m). Meta-regression analyses were used to assess the associations between 6MWD and NYHA functional class (Table 3). Significant difference between studies was present between class II and III (coefficient 67.4; 95% CI: 10.1 to 124.7, $P = 0.022$) and between class III and IV (coefficient 102.7; 95% CI: 13.0 to 192.4, $P = 0.026$). There was no significant difference between class I and II (coefficient 27.1; 95% CI: −39.8 to 93.9, $P = 0.422$). Adjusting for region, age, and sex did not change these associations. The estimated variance (τ^2) between studies was reduced from 10 480 to 7239 when all these variables were combined in the model (Table 3, Figure 3).

Discussion

This is the first study to systemically analyze the correlation between NYHA class and 6MWD. It demonstrates the subjectivity of the NYHA classification when compared with a more objective measure like the 6MWD, with the 6MWD in all NYHA classes showing significant heterogeneity across different studies. Despite this heterogeneity, worsening NYHA class status appears to correlate well with decreasing 6MWD between class II and III, and between class III and IV.

The basis of the NYHA classification stems from a patient's perceived and reported cardiac symptoms, as well the physician's assessment of these symptoms. This easy availability has resulted in its extensive use in numerous trials as well as guidelines. Some studies have shown the NYHA classification to be subjective. Surveys among physicians assessing NYHA class showed only about 54% to 56% concordance, giving a result little better than chance.[6,8] There was also no consistent method used to assess NYHA class with criteria ranging from self-reported walking distance to difficulty climbing stairs.[8] Self-reported walking distance has been shown to neither correlate with formally measured exercise capacity nor have any prognostic relevance.[8] Goode et al found significant difference in physician-rated and patient-rated NYHA class in a study of >1000 HF patients.[7] Severo et al also found discrepant interobserver thresholds of NYHA classification.[16]

In contrast, the 6MWD is a more objective test of a patient's functional capacity, requiring the patient to walk in a reproducible environment. The 6MWD has been shown in studies to have good prognostic value in the different subsets of HF patients. In a study of about 200 patients with mild to moderate HF, 6MWD was a strong predictor of mortality.[13] Castel et al showed that in patients with moderate to severe HF receiving cardiac resynchronization therapy, 6MWD was found to be an independent predictor of mortality.[17] Six-minute walk distance also strongly predicted mortality and HF rehospitalisations in patients hospitalized for acute HF.[18] However, the 6MWD is not without limitations. The test does not provide insight into the mechanisms of exercise limitation, and its results can be affected by a variety of factors unrelated to cardiopulmonary status, including age, sex, height, and weight. Some studies have shown that the change in 6MWD after the onset of therapy does not appear to predict outcomes in HF.[19] Other than 6MWD, cardiopulmonary exercise testing has often been used as the gold standard for functional assessment,[10] but this test requires appropriate equipment, trained staff, and logistical support and is relatively expensive. Several studies have shown the 6WMD to have similar utility and prognostic predictive value as CPET in patients with HF.[20,21] The appeal of the 6MWD stems from its reproducibilty, simplicity, and cost-effectiveness. However, the limitations of this test, as mentioned above, have to be considered.

In this study, the variation between NYHA class and 6MWD was comprehensively analyzed in 2 distinct

Table 2. Heterogeneity Within Each NYHA Class

NYHA Class	No. of Studies	No. of Patients	Pooled Average 6MWD, m (95% CI)	I^2, %	Q	*P* Value
I	16	984	420 (379 to 462)	98.4	934.2	<0.0001
II	24	2769	393 (362 to 424)	98.6	1657.6	<0.0001
III	29	1530	325 (296 to 354)	97.1	964.0	<0.0001
IV	7	139	225 (115 to 336)	97.6	248.4	<0.0001
Overall	35	5422	358 (338 to 379)	98.7	5580.1	<0.0001

Abbreviations: 6MWD, 6-minute walk distance; CI, confidence interval; NYHA, New York Heart Association.

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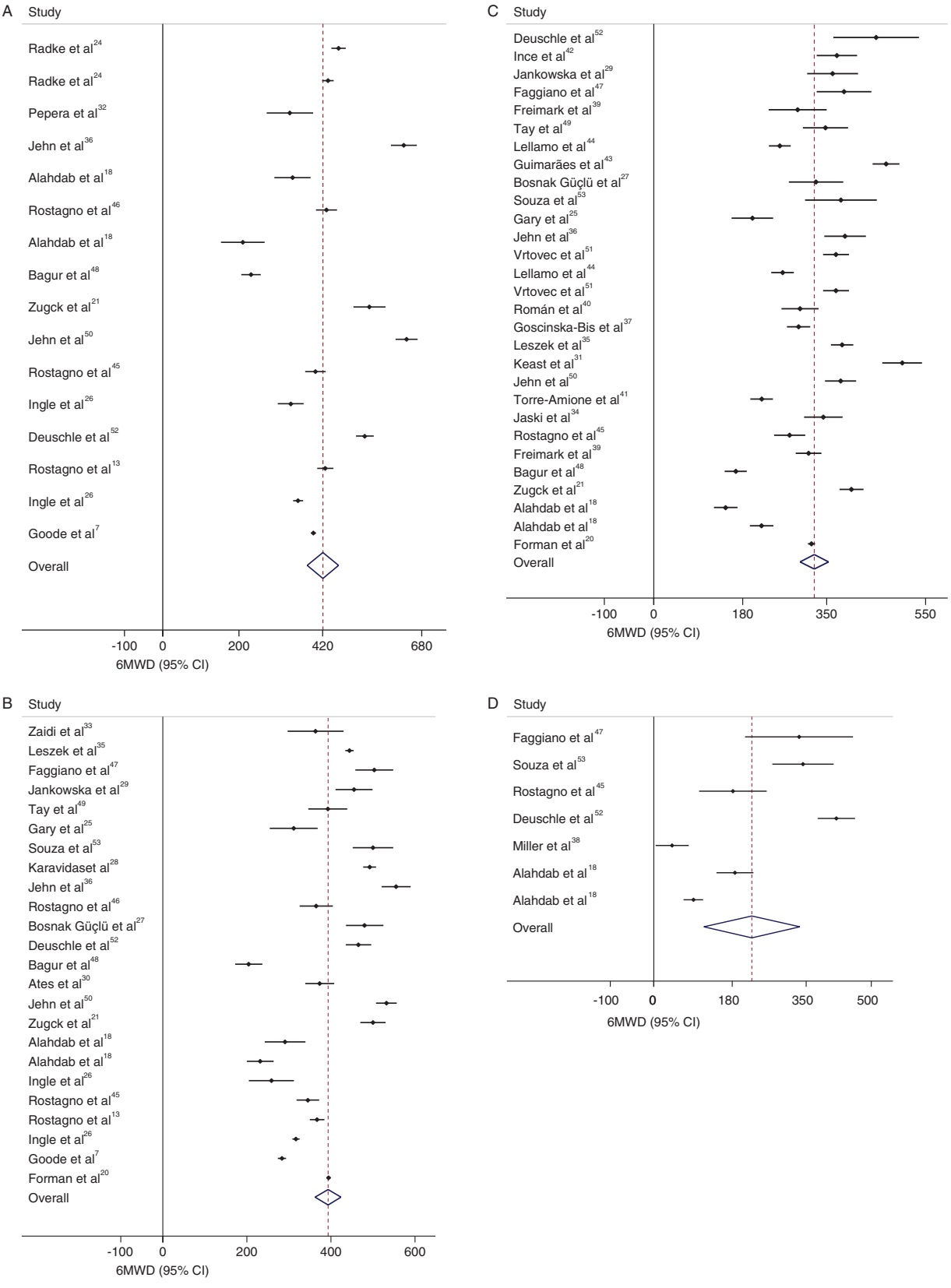

Figure 2. Distribution of 6MWD within NYHA, (A) class I, (B) class II, (C) class III, and (D) class IV. Abbreviations: 6MWD, 6-minute walk distance; CI, confidence interval; NYHA, New York Heart Association.

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Table 3. Comparison of 6MWD by NYHA Class

	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)[a]	*P* Value[a]
NYHA I vs II	27.1 (−39.8 to 93.9)	0.422	49.8 (−9.1 to 108.8)	0.096
NYHA II vs III	67.4 (10.1 to 124.7)	0.022	70.5 (21.6 to 119.3)	0.005
NYHA III vs IV	102.7 (13.0 to 192.4)	0.026	105.0 (25.5 to 184.5)	0.010

Abbreviations: 6MWD, 6-minute walk distance; CI, confidence interval; NYHA, New York Heart Association.
[a]Corrected for region, age, and sex.

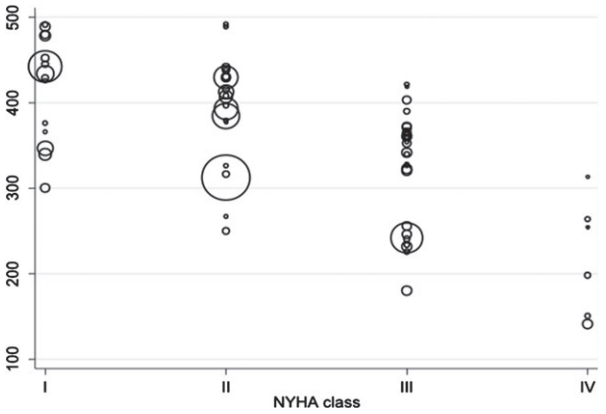

Figure 3. Comparison of 6MWD by NYHA class. Abbreviations: 6MWD, 6-minute walk distance; NYHA, New York Heart Association.

ways: within each NYHA class and between 2 adjacent NYHA classes. Comparing the different studies reporting 6MWD within each NYHA class, there was significant heterogeneity of 6MWD reported within all of the NYHA classes. Comparing the average 6MWD by NYHA class, there was no significant difference between class I and II, although there was a difference noted between class II vs III and class III vs IV. In this analysis, NYHA class appears useful for discriminating between mild and severe HF, but it may be more subjective in differentiating between mild and moderate HF. This has potential implications. Currently, various major guidelines, like the European[4] and American guidelines[22,23] for device therapy (eg, implantable cardioverter-defibrillator and cardiac resynchronization therapy), base their recommendations on the NYHA functional class. For example, implantable cardioverter-defibrillator therapy is recommended as a class I indication for primary prevention in NYHA II/III patients with impaired ejection fraction (EF), but it is not recommended for those with poor functional status.[22] Cardiac resynchronisation therapy is also recommended as a class I indication in suitable NYHA II/III and ambulatory NYHA IV patients, but not to those in NYHA I.[4,23] Differences in interpretation of NYHA class can result in a change in strength of indication for therapy from a class I recommendation to a lesser one. This conclusion appears mostly relevant for the group of patients who are asymptomatic/mildly symptomatic (NYHA I/II) and less so in more symptomatic HF patients (NYHA III/IV). Although NYHA classification is to some degree subjective, it is still an easily applied first-line tool in everyday clinical practice to assess patients' functional limitation. Moreover, in more symptomatic patients (NYHA III/IV), the NYHA classification appears to be a well-performing, accurate clinical tool to estimate these patients' functional limitation and guide therapy.

Study Limitations

Limitations of this study include the potential influence of other variables such as age, sex, comorbidities, and ethnicity on both NYHA class and 6MWD. Age and sex were corrected for in the analyses. For differences in ethnicity, an attempt to correct for this was made by considering the region of study. As data on comorbidities were not uniformly available in these reports, these could not be accounted for during the analysis. Differences between patients with reduced and preserved EF may exist. In the included studies that reported data on preserved EF,[24–26] these were not higher than those with reduced EF. Ingle et al reported similar 6MWD between both groups of patients.[26] Second, we would ideally have liked to compare both NYHA and 6MWD to cardiopulmonary exercise testing or clinical outcomes, but these were not available in all studies. Other limitations included lack of information on clinical significance of repeated measurements within each study.

Conclusion

Although there is an inverse correlation between NYHA class II to IV and 6MWD, there is significant heterogeneity across studies in reported 6MWD within each NYHA class and overlap in reported 6MWD between NYHA I and II. The NYHA classification appears to perform well in more symptomatic patients (NYHA III/IV) but less so in asymptomatic/mildly symptomatic patients (NYHA I/II). Nonetheless, the NYHA is an easily applied first-line tool in everyday clinical practice, but its potential subjectivity should be considered when performing comparisons across studies.

References

1. Criteria Committee of the New York Heart Association. Diseases of the heart and blood vessels. In: Harvey RM, et al, eds. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. 7th ed. Boston, MA: Little, Brown & Co.; 1973:286.
2. Castel MA, Magnani S, Mont L, et al. Survival in New York Heart Association class IV heart failure patients treated with cardiac resynchronization therapy compared with patients on optimal pharmacological treatment. *Europace*. 2010;12:1136–1140.
3. Muntwyler J, Abetel G, Gruner C, et al. One-year mortality among unselected outpatients with heart failure. *Eur Heart J*. 2002;23:1861–1866.

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22468

4. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on Cardiac Pacing and Resynchronization Therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Europace.* 2013;15:1070–1118.
5. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC [published correction appears in *Eur J Heart Fail.* 2013;15:361–362]. *Eur J Heart Fail.* 2012;14: 803–869.
6. Goldman L, Hashimoto B, Cook EF, et al. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale. *Circulation.* 1981;64:1227–1234.
7. Goode KM, Nabb S, Cleland JG, et al. A comparison of patient and physician-rated New York Heart Association class in a community-based heart failure clinic. *J Cardiac Fail.* 2008;14:379–387.
8. Raphael C, Briscoe C, Davies J, et al. Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. *Heart.* 2007;93:476–482.
9. Fedele F, Severino P, Calcagno S, et al. Heart failure: TNM-like classification. *J Am Coll Cardiol.* 2014;63:1959–1960.
10. Balady GJ, Arena R, Sietsema K, et al. Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation.* 2010;122:191–225.
11. Guyatt GH, Sullivan MJ, Thompson PJ, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J.* 1985;132:919–923.
12. Lee R, Chan YH, Wong J, et al. The 6-minute walk test predicts clinical outcome in Asian patients with chronic congestive heart failure on contemporary medical therapy: a study of the multiracial population in Singapore. *Int J Cardiol.* 2007;119:168–175.
13. Rostagno C, Olivo G, Comeglio M, et al. Prognostic value of 6-minute walk corridor test in patients with mild to moderate heart failure: comparison with other methods of functional evaluation. *Eur J Heart Fail.* 2003;5:247–252.
14. Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Smith GD, Altman DG, eds. *Systematic Reviews in Health Care: Meta-analysis in Context*. London, UK: BMJ Publishing Group; 2001:285–312.
15. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7:177–188.
16. Severo M, Gaio R, Lourenço P, et al. Indirect calibration between clinical observers—application to the New York Heart Association functional classification system. *BMC Res Notes.* 2011;4:276.
17. Castel MA, Méndez F, Tamborero D, et al. Six-minute walking test predicts long-term cardiac death in patients who received cardiac resynchronization therapy. *Europace.* 2009;11:338–342.
18. Alahdab MT, Mansour IN, Napan S, et al. Six minute walk test predicts long-term all-cause mortality and heart failure rehospitalization in African-American patients hospitalized with acute decompensated heart failure. *J Cardiac Fail.* 2009;15: 130–135.
19. Shah MR, Hasselblad V, Georghiade M, et al. Prognostic usefulness of the six-minute walk in patients with advanced congestive heart failure secondary to ischemic or nonischemic cardiomyopathy. *Am J Cardiol.* 2001;88:987–993.
20. Forman DE, Fleg JL, Kitzman DW, et al. 6-min walk test provides prognostic utility comparable to cardiopulmonary exercise testing in ambulatory outpatients with systolic heart failure. *J Am Coll Cardiol.* 2012;60:2653–2661.
21. Zugck C, Krüger C, Dürr S, et al. Is the 6-minute walk test a reliable substitute for peak oxygen uptake in patients with dilated cardiomyopathy? *Eur Heart J.* 2000;21:540–549.
22. Epstein AE, Dimarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: executive summary [published correction appears in *Heart Rhythm.* 2009;6:e1]. *Heart Rhythm.* 2008;5:934–955.
23. Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2013;61:e6–e75.
24. Radke KJ, King KB, Blair ML, et al. Hormonal responses to the 6-minute walk test in women and men with coronary heart disease: a pilot study. *Heart Lung.* 2005;34:126–135.
25. Gary RA, Sueta CA, Dougherty M, et al. Home-based exercise improves functional performance and quality of life in women with diastolic heart failure. *Heart Lung.* 2004;33:210–218.
26. Ingle L, Cleland JG, Clark AL. Perception of symptoms is out of proportion to cardiac pathology in patients with "diastolic heart failure." *Heart.* 2008;94:748–753.
27. Boşnak Guçlu M, Inal İnce D, Arıkan H, et al. A comparison of pulmonary function, peripheral and respiratory muscle strength and functional capacity in the heart failure patients with different functional classes [article in Turkish]. *Anadolu Kardiyol Derg.* 2011;11:101–106.
28. Karavidas A, Parissis JT, Matzaraki V, et al. Functional electrical stimulation is more effective in severe symptomatic heart failure patients and improves their adherence to rehabilitation programs. *J Cardiac Fail.* 2010;16:244–249.
29. Jankowska EA, Wegrzynowska K, Superlak M, et al. The 12-week progressive quadriceps resistance training improves muscle strength, exercise capacity and quality of life in patients with stable chronic heart failure. *Int J Cardiol.* 2008;130:36–43.
30. Ates I, Yavuz AH, Doğru M, et al. Effects of ivabradine on 6-minute walk test and quality of life in patients with previously implanted CRT-D. *J Investig Med.* 2013;61:1013–1017.
31. Keast ML, Slovinec D'Angelo ME, Nelson CR, et al. Randomized trial of Nordic walking in patients with moderate to severe heart failure. *Can J Cardiol.* 2013;29:1470–1476.
32. Pepera GK, Sandercock GR, Sloan R, et al. Influence of step length on 6-minute walk test performance in patients with chronic heart failure. *Physiotherapy.* 2012;98:325–329.
33. Zaidi AN, White L, Holt R, et al. Correlation of serum biomarkers in adults with single ventricles with strain and strain rate using 2D speckle tracking. *Congenit Heart Dis.* 2013;8:255–265.
34. Jessup M, Greenberg B, Mancini D, et al. Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID): a phase 2 trial of intracoronary gene therapy of sarcoplasmic reticulum Ca2 + −ATPase in patients with advanced heart failure. *Circulation.* 2011;124:304–313.
35. Leszek P, Klisiewicz A, Janas J, et al. Usefulness of 6-minute walk test, plasma neurohumoral and cytokine activation in the assessment of symptomatic patients with left ventricle dysfunction caused by chronic severe mitral valve regurgitation. *Acta Cardiol.* 2010;65:43–51.
36. Jehn M, Schmidt-Trucksäss A, Schuster T, et al. Accelerometer-based quantification of 6-minute walk test performance in patients with chronic heart failure: applicability in telemedicine. *J Cardiac Fail.* 2009;15:334–340.
37. Goscinska-Bis K, Bis J, Krejca M, et al. Totally epicardial cardiac resynchronization therapy system implantation in patients with heart failure undergoing CABG. *Eur J Heart Fail.* 2008;10:498–506.
38. Miller LW, Pagani FD, Russell SD, et al; HeartMate II Clinical Investigators. Use of a continuous-flow device in patients awaiting heart transplantation. *N Engl J Med.* 2007;357:885–896.
39. Freimark D, Shechter M, Schwamenthal E, et al. Improved exercise tolerance and cardiac function in severe chronic heart failure patients undergoing a supervised exercise program. *Int J Cardiol.* 2007;116:309–314.
40. Román A, Gispert P, Monforte V, et al. Long-term outcomes of treatment with bosentan in pulmonary hypertension [article in Spanish]. *Arch Bronconeumol.* 2006;42:616–620.
41. Torre-Amione G, Sestier F, Radovancevic B, et al. Broad modulation of tissue responses (immune activation) by celacade

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DOI:10.1002/clc.22468

may favorably influence pathologic processes associated with heart failure progression. *Am J Cardiol.* 2005;95:30C–40C.
42. Ince H, Petzsch M, Rehders TC, et al. Transcatheter transplantation of autologous skeletal myoblasts in postinfarction patients with severe left ventricular dysfunction. *J Endovasc Ther.* 2004;11:695–704.
43. Guimãraes GV, Bellotti G, Bacal F, et al. Can the cardiopulmonary 6-minute walk test reproduce the usual activities of patients with heart failure? [article in English, Portuguese]. *Arq Bras Cardiol.* 2002;78:553–560.
44. Iellamo F, Volterrani M, Caminiti G, et al. Testosterone therapy in women with chronic heart failure: a pilot double-blind, randomized, placebo-controlled study. *J Am Coll Cardiol.* 2010;56:1310–1316.
45. Rostagno C, Galanti G, Comeglio M, et al. Comparison of different methods of functional evaluation in patients with chronic heart failure. *Eur J Heart Fail.* 2000;2:273–280.
46. Rostagno C, Galanti G, Felici M, et al. Prognostic value of baroreflex sensitivity assessed by phase IV of Valsalva manoeuvre in patients with mild-to-moderate heart failure. *Eur J Heart Fail.* 2000;2:41–45.
47. Faggiano P, D'Aloia A, Gualeni A, et al. Assessment of oxygen uptake during the 6-minute walking test in patients with heart failure: preliminary experience with a portable device. *Am Heart J.* 1997;134(2 part 1):203–206.
48. Bagur R, Rodés-Cabau J, Dumont E, et al. Performance-based functional assessment of patients undergoing transcatheter aortic valve implantation. *Am Heart J.* 2011;161:726–734.
49. Tay EL, Papaphylactou M, Diller GP, et al. Quality of life and functional capacity can be improved in patients with Eisenmenger syndrome with oral sildenafil therapy. *Int J Cardiol.* 2011;149:372–376.
50. Jehn M, Schmidt-Trucksäss A, Schuster T, et al. Pedometer accuracy in patients with chronic heart failure. *Int J Sports Med.* 2010;31:186–191.
51. Vrtovec B, Poglajen G, Lezaic L, et al. Comparison of transendocardial and intracoronary CD34+ cell transplantation in patients with nonischemic dilated cardiomyopathy. *Circulation.* 2013;128(11 suppl 1):S42–S49.
52. Deuschle K, Weinert K, Becker MO, et al. Six-minute walk distance as a marker for disability and complaints in patients with systemic sclerosis. *Clin Exp Rheumatol.* 2011;29(2 suppl 65):S53–S59.
53. Souza R, Jardim C, Julio Cesar Fernandes C, et al. NT-proBNP as a tool to stratify disease severity in pulmonary arterial hypertension. *Respir Med*. 2007;101:69–75.

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