ORIGINAL ARTICLE

# EFFECT OF DYSPNEA ON THE 1-YEAR SURVIVAL OF PATIENTS WITH PROGRESSIVE DISEASE AT CIPTO MANGUNKUSUMO HOSPITAL

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## ABSTRACT

Background: Dispnea as a subjective sensation is a sign of certain underlying disease which need to be diagnosed and treated to prevent the mortality, especially in patients with progressive disease. Previous study has shown that patients with dyspnea at admission have higher mortality.

Objective: To determine the association between dyspnea with 1 year survival in patients with progressive disease who were admitted to RSCM. Methods: A retrospective cohort study was conducted by tracing the medical records of 155 patients with progressive disease who were hospitalized at RSCM during August 2018 until December 2019. Recruited subjects were adults patients who 18 years above diagnosed with COPD, heart failure, malignancy or CVD. Identity, dispnea, and survival data were collected through medical records. Statistical analysis was conducted by using multivariate and Kaplan Meier analysis using SPSS software. Results: In this study, the survival rate of patients with progressive disease who were admitted to RSCM in August 2018-December 2019 was 34.8% with a mean survival of 163 days and a median survival of 72 days. Among the patients 49% had dyspnea. The survival rate of patients with dispnea was 11% with a mean survival of 115 days and a median survival of 29 days. Dyspnea was significantly associated with survival with p < 0,05 and adjusted HR 1.928 (95% CI: 1.225 - 3.03). In the subgroup analysis of heart failure, malignancy, and CVD, dispnea was associated with survival with p<0,05 and the HR value for every group 16,59 (95% CI: 2,20 – 124,73), 2,18 (95% CI: 1,33 – 3,58), and 2,90 (95% CI: 1,34 – 6,28). Conclusion: Dyspnea has significant association with survival.

**Key words:** dyspnea, progressive disease, survival.

## ABSTRAK

Latar belakang: Dispnea sebagai sensasi subjektif yang dialami pasien merupakan penanda adanya penyakit dasar yang perlu didiagnosis dan ditatalaksana, khususnya pada pasien dengan penyakit progresif. Studi sebelumnya telah menunjukkan bahwa keluhan dispnea saat admisi berkaitan dengan peningkatan mortalitas pasien.

Tujuan: Mengetahui pengaruh dispnea terhadap kesintasan 1 tahun pada pasien dengan penyakit progresif di RSCM.

Metode: Studi kohort retrospektif dilakukan dengan menelusuri rekam medik 155 pasien dengan penyakit progresif yang dirawat inap di RSCM selama bulan Agustus 2018 hingga Desember 2019. Sampel penelitian ada pasien dewasa usia 18 tahun ke atas yang didiagnosa PPOK, gagal jantung, keganasan atau CVD. Data identitas, keluhan dispnea dan kesintasan dikumpulkan melalui rekam medis kemudian dianalisis menggunakan analisis multivariat dan grafik Kaplan Meier menggunakan perangkat SPSS.

Hasil: Pada penelitian ini didapatkan kesintasan subjek dengan penyakit progresif yang dirawat di RSCM pada bulan Agustus 2018 hingga Desember 2019 sebesar 34,8% dengan mean survival sebesar 163 hari dan median survival sebesar 72 hari. Sebanyak 49% subjek memiliki keluhan dispnea. Kesintasan subjek dengan dispnea sebesar 11%, dengan mean dan median survival sebesar 115 hari dan 29 hari. Dispnea berhubungan secara signifikan terhadap kesintasan dengan nilai p < 0,05 dan adjusted HR 1,928 (95% CI: 1,225 – 3,03). Pada subgroup analysis kelompok subjek gagal jantung, keganasan, dan CVD, didapatkan dispnea berhubungan dengan kesintasan dengan nilai p<0,05 dan nilai HR masing-masing 16,59 (95% CI: 2,20 – 124,73), 2,18 (95% CI: 1,33 – 3,58), dan 2,90 (95% CI: 1,34 – 6,28). Kesimpulan: Dispnea memiliki hubungan yang signifikan dengan kesintasan.

**Kata kunci:** dispnea, penyakit progresif, kesintasan.

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**EFFECT OF DYSPNEA ON THE 1-YEAR SURVIVAL OF PATIENTS WITH PROGRESSIVE DISEASE AT CIPTO MANGUNKUSUMO HOSPITAL**

## BACKGROUND

Dyspnea is a subjective sensation of uncomfortable breathing. It is mostly caused by impairment in cardiovascular and respiratory system but could also be caused by neuromuscular and psychological problems. Dyspnea seldom studied to predict mortality due to its subjective nature. Moreover, clinicians often unaware and ignore patient's complaint of dyspnea. It is unfortunate since dyspnea is one of the signs of serious illness. Patients with progressive disease such as chronic obstructive pulmonary disease (COPD), malignancy, heart failure, and cerebrovascular disease often complaint of dyspnea. About 41,2% patients with progressive disease complaint of dyspnea and 29,6% felt depressed due to this condition.[1,2]

Previous studies showed that dyspnea was associated with mortality. Study in Japan showed that patients complaining dyspnea during admission had 1,37 higher mortality compared to normal population.[3] Other study conducted in Wales reported higher mortality hazard ratio as dyspnea progress.[4] A cohort study in America reported dyspnea as an independent all-cause mortality predictor.[5] The objective of this study wasto determine the association between dyspnea with 1 year survival in patients with progressive disease who were admitted to RSCM.

## METHODS

This study is a retrospective cohort study. Subjects were progressive disease patient with/without complaint of dyspnea hospitalized in Cipto Mangunkusumo hospital. Minimal number of samples needed for this study is 150 samples. Multivariate analysis with logistic regression was performed to assess variables that associated with survival. Hosmer and Lemeshow test were performed to assess the calibration of gold standard equation obtained from logistic regression. Discrimination performance was assessed by area under the curve (AUC). Effect size and statistical calculation for this study was odd ratio and hazard ratio with confidence interval of 95%. Survival analysis was performed to evaluate mean and median survival time for each group.

## RESULTS

A total of 155 subjects were involved in this study. The proportion of male subjects was 47,1% while female was 52,9%. Subjects had an mean age of 58,3 years with 49% subjects aged ≥60 years and 51% aged <60 years. Total subjects with heart failure, COPD, malignancy, cerebrovascular disease, and pneumonia were 29%, 8,4%, 57,4%, 73,5%, and 51% respectively. The median of length of stay is 11 days and median survival time is 72 days. After 1 year, 34,8% subjects were still alive.

Bivariate analysis showed that dyspnea, heart failure, malignancy, and pneumonia had significant association with survival. Multivariate analysis with logistic regression showed that dyspnea, pneumonia, and heart failure fulfill the criteria for gold standard model.

Hosmer and Lemeshow test showed p = 0,713 which meant that the equation had good calibration. AUC analysis was 78,4% (IC 95%: 70,8%-86,0%) with p < 0,005. AUC score 78,4% is considered in moderate category (70-80%) which meant this equation could differentiate between dead and alive outcome.

**Table 1.** Patient's characteristics

| Characteristics | Frequency (Percentage) | Mean/Median (SD/IQR) |
|---|---|---|
| Gender | | |
| Male | 73 (47,1) | |
| Female | 82 (52,9) | |
| Age* | | 58,3 (±15,2) |
| ≥60 years | 76 (49,0) | |
| <60 years | 79 (51,0) | |

| | | |
|---|---|---|
| Dyspnea | | |
| Yes | 76 (49,0) | |
| No | 79 (51,0) | |
| Heart failure | | |
| Yes | 45 (29,0) | |
| No | 110 (71,0) | |
| COPD | | |
| Yes | 13 (8,4) | |
| No | 142 (91,6) | |
| Malignancy | | |
| Yes | 89 (57,4) | |
| No | 66 (42,6) | |
| Cerebrovascular disease | | |
| Yes | 41 (73,5) | |
| No | 114, (26,5) | |
| Pneumonia | | |
| Yes | 79 (51,0) | |
| No | 76 (49,0) | |
| Number of progressive diseases | 126 (81,3) | |
| 1 disease | 25 (16,1) | |
| 2 diseases | 4 (2,6) | |
| 3 diseases | | |
| Outcome after 1 year following hospitalization | | |
| Dead | 101 (65,2) | |
| Alive | 54 (34,8) | |
| Respiration rate* | | 26 times/minute (26-20) |
| Length of stay* | | 11 days (19-6) |
| *Survival time** | | 72 days (365-17) |

*Data with abnormal distribution will be shown in median and IQR

**Table 2.** Multivariate analysis with logistic regression

| Variable | B (constant coefficient) | Standard error | Adjusted OR | CI 95% | | p |
|---|---|---|---|---|---|---|
| | | | | Min | Max | |
| Dyspnea | 1,35 | 0,46 | 3,88 | 1,55 | 9,70 | 0,004 |
| Pneumonia | 1,20 | 0,42 | 3,33 | 1,43 | 7,72 | 0,005 |
| Heart failure | -1,95 | 0,46 | 0,14 | 0,05 | 0,35 | 0,001 |
| Constanta | -0,029 | 2,91 | 0,97 | | | 0,92 |

Based on logistic regression, the obtained equation was:

$$Y = -0,029 + 1,35\ (\text{Dyspnea}) + 1,20\ (\text{Pneumonia}) - 1,95\ (\text{Heart failure})$$

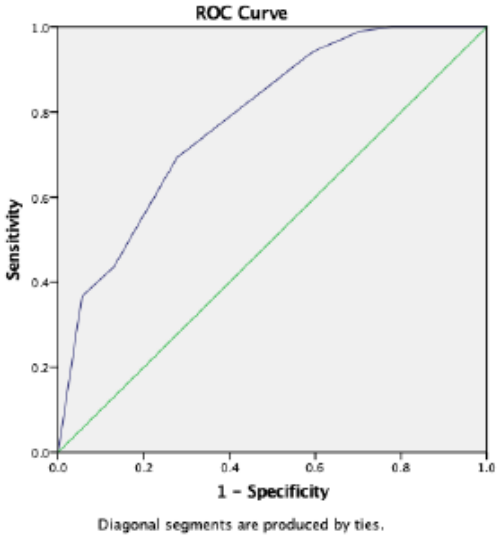


**Figure 1.** AUC graphic from logistic regression equation

**Table 3.** Mean and median survival time of every groups

| Variable | Mean Survival Time | Median Survival Time |
|---|---|---|
| Dyspnea | | |
| Yes | 115 days | 29 days |
| Nos | 213 days | 270 days |
| Pneumonia | | |
| Yes | 107 days | 28 days |
| No | 222 days | -* |
| Heart failure | | |
| Yes | 241 days | 132 days |
| No | -* | 32 days |
| Malignancy | | |
| Yes | 127 days | 32 days |
| No | 212 days | 263 days |
| Cerebrovascular disease | | |
| Yes | 167 days | 133 days |
| No | 162 days | 62 days |
| COPD | | |
| Yes | 185 days | 108 days |
| No | 161 days | 63 days |

*still not achieved until the end of follow up

We performed survival analysis on every groups. The overall mean and median survival team were 163 days and 72 days. Mean and median survival time of each group can be seen on table 4. We perform hazard ratio (HR) analysis with cox regression for the gold standard model. The adjusted HR from highest to lowest was dyspnea, pneumonia, and heart failure.

**Table 4.** Hazard ratio with *cox regression*

| Variable | Adjusted HR | CI 95% | | p |
|---|---|---|---|---|
| | | Min | Max | |
| Dyspnea | 1,93 | 1,23 | 3,03 | 0,005 |
| Pneumonia | 1,93 | 1,22 | 3,04 | 0,005 |
| Heart failure | 0,35 | 0,21 | 0,58 | 0,001 |

In this study we perform survival analysis with Kaplan Meier graphic presentation (figure 2). In the Kaplan Meier graphic figure 2 we can see that Proportional Hazard assumption is fulfilled. Mean and median survival are 163 days and 72 days. For the dyspnea group, mean and median survival are 115 days and 29 days, while non dyspnea group have mean and median survival of 213 days and 270 days.

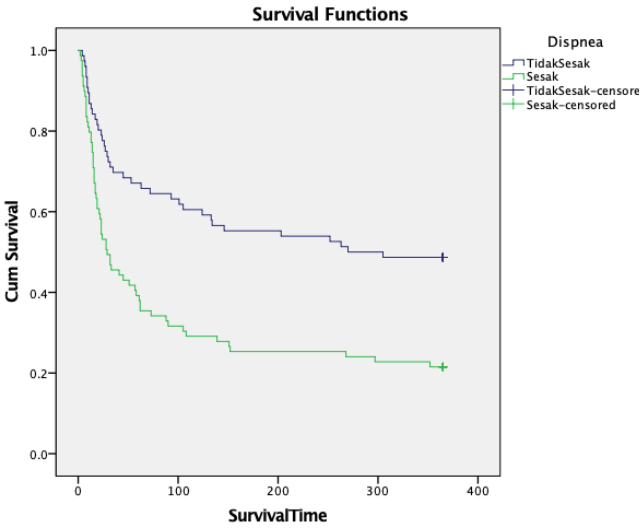


**Figure 2**. Dyspnea Survival

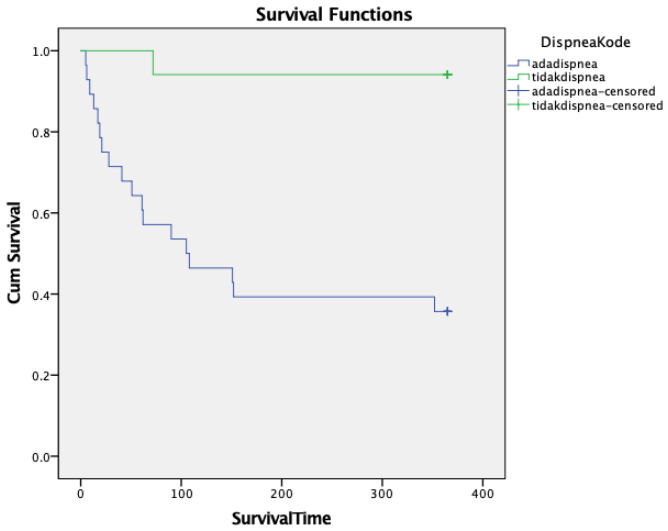


**Figure 3.** Dyspnea Survival in the Heart Failure Subgroup

We also perform subgroup analysis for every progressive disease to see the association between dyspnea and survival.

**Table 5**. RR and HR Analysis in Heart Failure Subgroup

| Variable | RR (95%CI) | *P* | HR (95%CI) | *P* |
|---|---|---|---|---|
| **Dyspnea** | 10,92 (1,60 – 74,64) | 0,001 | 16,59 (2,20 – 124,73) | 0,006 |

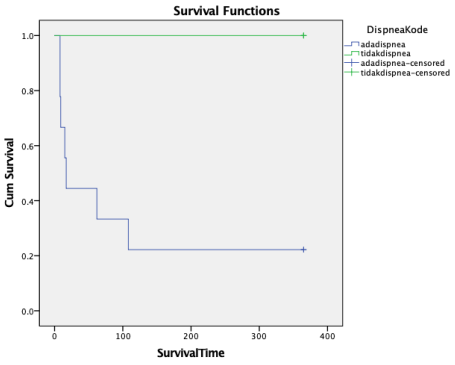


**Figure 4**. Dyspnea Survival in COPD Subgroup

**Table 6**. RR and HR Analysis in the Heart Failure Subgroup

| Variable | RR (95%CI) | *P* | HR (95%CI) | *P* |
|---|---|---|---|---|
| **Dyspnea** | NA | NA | 52,28 (0,98 – 27958,95) | 0,21 |

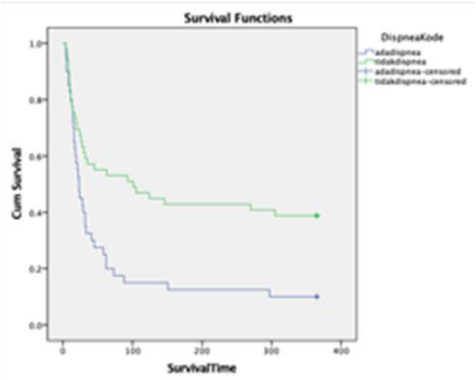


**Figure 5.** Dyspnea Survival in Malignancy

**Table 7**. RR and HR Analysis in Malignancy Subgroup

| Variable | RR (95%CI) | *P* | HR (95%CI) | *P* |
|---|---|---|---|---|
| **Dyspnea** | 1,47 (1,15 – 1,87) | 0,002 | 16,59 (2,20 – 124,73) | 0,006 |

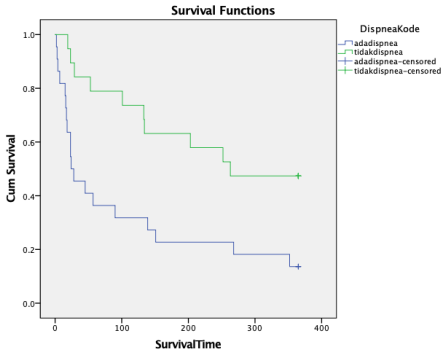


**Figure 6**. Dyspnea Survival in CVD Subgroup.

**Table 8**. RR and HR Analysis in CVD Subgroup.

| Variable | RR (95%CI) | *P* | HR (95%CI) | *P* |
|---|---|---|---|---|
| **Dyspnea** | 1,64 (1,03 – 2,59) | 0,018 | 2,90 (1,34 – 6,28) | 0,006 |

## DISCUSSION

Bivariate analysis showed that there were a few variables significantly associated with survival. These variables were dyspnea (OR 3,46, 95% CI: 1,71-69,6), heart failure (OR 0,25, 95% CI: 0,12-0,51), malignancy (OR 2,54, 95% CI: 1,29-5,0), and pneumonia (OR 4,49, 95% CI: 2,18-9,24). Multivariate analysis with logistic regression showed 3 variables significantly associated with survival, which is dyspnea (aOR 3,88, 95% CI: 1,55-97,0), pneumonia (aOR 3,33, 95% CI: 1,43-7,72), and heart failure (aOR 0,14, 95% CI: 0,05-0,35). The result of this study was similar to previous studies reporting there were association between dyspnea and mortality. Increased respiration rate during hospital admission was associated with poorer clinical outcomes.[6] Vonderbank et al. reported that patient with acute and chronic hypercapnic had higher 1 year mortality compared to normocapnic patient (32% and 20,2% compared to 14,5%).[7]

Mentz et al. performed a study involving 48.616 patients with acute heart failure to assess the relation between dyspnea and mortality. Worse degree of dyspnea severity was associated with higher mortality, 6,3% in patient with dyspnea during moderate activity, 7,6% in patient with dyspnea during light activity, and 11,6% patient with dyspnea during rest. Dyspnea during rest was also associated with higher 30 days mortality, rehospitalization due to heart failure, longer length of stay, and increased health insurance payment compared to group with dyspnea during moderate activity.[8]

The adjusted HR of dyspnea for survival was 1,93 (CI 95%: 1,23-3,03). Result of this study was similar to previous studies. Tessier et al. performed a study involving 2.762 patients aged >65 years old with dyspnea. Dyspnea was classified as grade 1-5 based on medical research council (MRC) questionnaire. Study by Tessier et al. showed that dyspnea was an independent predictor of mortality, especially on groups with dyspnea grade 3 (aHR 1,4, 95% CI: 1,2-1,7), grade 4 (aHR 2,0, 95% CI: 1,6-2,5), and grade 5 (aHR 6,0, 95% CI: 3,7-9,7).[9] Every increase of 1 MRC score was correlated with increased HR.[10] Study by Nakanishi et al. showed that patient with dyspnea (HR 2,0, 95% CI: 1,0-4,0) had higher mortality compared to patient with typical angina (HR 1,1, 95% CI: 0,6-2,3).[11] Abidov et al. reported that patient with dyspnea had risk of myocardial death 4 times higher compared to asymptomatic patient and 2 times higher than patient with typical angina.[12]

The aOR of heart failure for survival is 0,14 (95% CI: 0,05-0,35) which showed that heart failure is a protective factor for survival. The HR of heart failure for survival is 0,35 (95% CI: 0,21-0,58). These results greatly differ from other studies that reported heart failure increased patient mortality. This difference might be caused by 2 reasons. First, the patients who were not included in heart failure group is included in

malignancy, cerebrovascular disease, or COPD groups. All 3 groups included other progressive disease patients with different mortality rate. Second, this research was performed in referral hospital with advanced facility for heart care. Patient with heart failure were given proper and adequate treatment therefore increasing their survival.

In this study, the survival rate of patients with progressive disease who were admitted to RSCM in August 2018-December 2019 was 34.8% with a mean survival of 163 days and a median survival of 72 days. Among the patients 49% had dyspnea. The survival rate of patients with dyspnea was 11% with a mean survival of 115 days and a median survival of 29 days. Dyspnea was significantly associated with survival with p < 0,05, RR 1,52 (95%CI: 1,19 – 1,95) adjusted OR 3.88 (95% CI: 1.55 - 9.70) and adjusted HR 1.928 (95% CI: 1.225 - 3.03). Pneumonia also had a significant association to survival with adjusted OR 3.33 (95% CI: 1.43 - 7.72) and adjusted HR 1.926 (95% CI: 1.220 - 3.04). In the subgroup analysis of heart failure, malignancy, and CVD, dyspnea was associated with survival (p<0,05) and the HR value for every group 16,59 (95% CI: 2,20 – 124,73), 2,18 (95% CI: 1,33 – 3,58), and 2,90 (95% CI: 1,34 – 6,28).

**STRENGTH AND LIMITATION OF THE STUDY**

This study is the first study assessing the relation between dyspnea and survival in patient with progressive disease. There were various variable related to dyspnea included in this study so the result of this study was minimally affected by confounding factors. The limitation of this study is sampling method by convenient sampling which might increase selection bias.

**CONCLUSION**

Dyspnea could be used to help clinician predict survival in patient with progressive disease.

**REFERENCES**


1. Damani A, Ghoshal A, Salins N, Deodhar J, Muckaden M. Prevalence and Intensity of Dyspnea in Advanced Cancer and its Impact on Quality of Life. Indian J Palliat Care. 2018;24(1):44–50.
2. Dhingra L, Barrett M, Knotkova H, Chen J, Riggs A, Lee B, et al. Symptom Distress Among Diverse Patients Referred for Community-Based Palliative Care: Sociodemographic and Medical Correlates. J Pain Symptom Manage. 2018;55(2):290–6.
3. Pesola GR, Ahsan H. Dyspnea as an Independent Predictor of Mortality. Clin Respir J. 2016;10(2):142–52.
4. Intelligence WC, Unit S, Wales PH. Dyspnoea and mortality in older people in the community: a 10-year follow-up. 2004;545–9.
5. Figarska S, Boezen H, Vonk J. Dyspnea severity, changes in dyspnea status and mortality in the general population : the

Vlagtwedde / Vlaardingen study. Eur J Epidemiol. 2012;27(11):867–76.

6. Strauß R, Ewig S, Richter K, König T, Heller G, Bauer TT. The prognostic significance of respiratory rate in patients with pneumonia: a retrospective analysis of data from 705,928 hospitalized patients in Germany from 2010-2012. Dtsch Arztebl Int. 2014;111:503–508.
7. Vonderbank S, Gibis N, Schulz A, Boyko M, Erbuth A, Gürleyen H, et al.. Hypercapnia at Hospital Admission as a Predictor of Mortality. Open Access Emerg Med. 2020 Jun 26;12:173-180. doi: 10.2147/OAEM.S242075
8. Mentz RJ, Mi X, Sharma PP, Qualls LG, DeVore AD, Johnson KW,et al. Relation of dyspnea severity on admission for acute heart failure with outcomes and costs. Am J Cardiol. 2015 Jan 1;115(1):75-81. doi: 10.1016/j.amjcard.2014.09.048.
9. Tessier JF, Nejjari C, Letenneur L, Filleul L, Marty ML, Gateau PB, et al.. Dyspnea and 8- year mortality among elderly mean and women: the PAQUID cohort study. European J Epidemiol. 2001; 17:223–229.
10. Huijnen B, van der Horst F, van Amelsvoort L, Wesseling G, Lansbergen M, Aarts P, et al. Dyspnea in elderly family practice patients. Occurrence, severity, quality of life and mortality over an 8-year period. Family Practice. 2006; 23(6):34–39.
11. Nakanishi R, Gransar H, Rozanski A, Rana JS, Cheng VY, Thomson LEJ, et al. Dyspnea predicts mortality among patients undergoing coronary computed tomographic angiography. Int J Cardiovasc Imaging. 2016;32(2):329–37.
12. Abidov A, Rozanski A, Hachamovitch R, Hayes SW, Aboul- Enein F, Cohen I, et al. Prognostic significance of dyspnea in patients referred for cardiac stress testing. N Engl J Med. 2005; 353:1889–1898