RESPIRATORY CARE Paper in Press. Published on January 15, 2013 as DOI: 10.4187/respcare.02290

Title: Prognostic significance of distance, work, oxygen saturation and dyspnea during 6-minute walk test in COPD patients.

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The authors report no conflicts of interest.

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Abstract:

Background: Distance walked during the six-minute walk test (6MWT) predicts mortality in chronic obstructive pulmonary disease (COPD). The body weight of the patient affects the work required to walk. Calculated work during the 6MWT (6MWORK) may account for differences in walking distance resulting from change in body weight. Thus, 6MWORK might be a better predictor of mortality than distance walked. This study was designed to test this hypothesis and to assess if other variables measured during the 6MWT, like continuous oximetry recording, offered additional prognostic information.

Methods: retrospective analysis of prospectively collected data, 104 COPD patients were studied. 6MWT was performed in all cases. 6MWORK was calculated as body weight (in kgs.) X distance walked (in meters). Receiver-operating characteristics curves were used to assess the value of variables to predict mortality. Additional analysis was performed using Kaplan-Meier survival plots and Cox proportional hazards regression models.

Results: Mean follow-up: 590 ± 472 days.Eleven patients (10.6%) died. 6MWORK was not better than distance walked to predict mortality (AUC: 0.77 for 6MWORK vs 0.80 for distance; difference: 0.030, 95% CI: -0.054 to 0.121, $p = 0.448$) . Patients who died had more dyspnea (measured using Borg scale) after the 6MWT (8.5 vs 4.0, $p < 0.001$), lower basal SaO_2 (85% vs 93%, $p = 0.001$), worse oxygen saturation during the 6MWT (mean SaO2 while walking 74.0% vs 86.6%, $p = 0.015$) and walked less distance (255 vs 480 m, $p = 0.0013$). On multivariate analysis, only 6MWT distance and dyspnea after the test correlated independently with mortality ($p = 0.005$ for both variables).

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Conclusions: 6MWORK was not more useful than 6MWT distance to predict mortality. The study confirms that 6MWT distance and dyspnea on exertion are key elements in prognostic evaluation in COPD, while the value of exercise oxygen desaturation is less clear.

Key words: six-minute walk test; prognosis; mortality; pulmonary diseases, chronic obstructive; work capacity evaluation; oximetry.

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Introduction:

Chronic obstructive pulmonary disease (COPD) is an important cause of mortality. Several factors have been found to predict adverse outcome in this disease, like degree of dyspnea, exercise capacity, body mass index (BMI) and degree of airway obstruction, as measured using FEV_1.[1] The six-minute walk test (6MWT) is an easy to perform submaximal exercise test that reflects the functional exercise capacity in COPD patients, and the distance walked during the test correlates strongly with mortality in this disease.[2-4] Oxygen desaturation during the 6MWT might add a modest additional prognostic information in COPD.[4,5] However, measurement of oxygen saturation during the test is not a standardized procedure[6]. In many cases, when oxygen saturation is determined, only punctual measurements are taken, and the examiner only report whether the saturation falls below 90%. Continuous oximetry recording during the 6MWT might offer a better estimate of gas exchange during exercise and, thus, might correlate better with prognosis.

The body weight of the patient affects the work/energy required to perform the walk.[7] As the 6MWT is intended to account for work, and work is determined by force and distance traveled, it would be logical to include force (body weight) as well as distance when assessing the results of the 6MWT. Carter et al suggested that calculated work (body weight X distance walked) during the 6MWT (6MWORK) may account for differences in walking distance resulting from change in body weight, and this parameter would therefore improve the usefulness of the test.[7] We hypothesized that 6MWORK might be a better predictor of mortality in COPD patients than distance walked. This study was designed with the main objective of testing this hypothesis. Secondary objectives were to determine if other parameters measured during the 6MWT offered additional prognostic information, with a special focus on variables derived from continuous oximetry recording during exercise.

Material and Methods:

Patients and study design:

This is a retrospective analysis of prospectively collected data. Patients were recruited from the Respiratory Medicine service of the University Hospital Lucus Augusti. The study population included patients in which 6MWT was performed as part of their clinical evaluation, according to the criteria of their attending clinician. Inclusion criteria were age > 40 years, FEV_1/FVC < 70% and postbronchodilator FEV_1 < 80% of predicted value, and clinical stability for at least 8 weeks. Exclusion criteria were diagnosis of asthma, malignant disorders, uncontrolled heart failure, coexisting respiratory disorders (e.g: kyphoscoliosis) and inability to perform spirometry and/or 6MWT. Approval for the use of the data was obtained from our local ethical committee.

Spirometry was performed on a Sibelmed Datospir 120 spirometer (Sibel S.A, Barcelona, Spain), according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) consensus guidelines,[8] and using the ERS predicted values.[9] The 6MWT was performed according to the ATS statement, in a 30 m corridor.[6] For patients who were already on long-term oxygen therapy, the 6MWT was performed with supplemental oxygen at their usual flow. Continuous pulse oximetry was recorded during the test using a wrist oximeter with a finger probe (Pulsox 3i; Minolta, Ramsey, N.J. USA). Pulse oximetry variables were calculated using computer software (Pulsox SaO_2 analysis software DS-3; Minolta, Ramsey, N.J., USA). We registered the

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following variables: total distance walked, resting SaO_2 before walking, mean and lower SaO_2 during the test, dyspnea and leg fatigue after the test as measured using the modified Borg scale, and cumulative percentages of time at saturation below 90% (CT90) while walking. 6MWORK was calculated as body weight (in kgs.) X distance walked (in meters).

Statistical analysis:

The primary endpoint was the time from the date of the 6MWT to the date of death. The patients were censored at the end of the study if still alive. Vital status, ascertained as of July 2012 was determined by review of electronic patient charts. Normal distribution of data was assessed using the D'Agostino-Pearson test. Data are expressed as mean ± SD (normal distribution) or as median (interquartile range) (non normal distribution) for continuous variables, and as percentages for categorical variables. Correlation between variables was assessed with Pearson's or Spearman's correlation coefficients, as appropriate. For continuous variables, comparisons between survivors and non-survivors were made using unpaired t-test or Wilcoxon rank-sum test, as appropriate. Chi-square test was used for categorical variables. Receiver-operating characteristics (ROC) curves were constructed to assess the value of different variables to predict mortality. Differences in areas under the different curves were calculated using the method of Delong et al.[10] Kaplan-Meier cumulative survival plots were obtained, for variables with the highest areas under the ROC curves. Kaplan-Meier plots were constructed for values above and below the value with the best combination of sensitivity and specificity in ROC analysis. Log Rank test was used to compare survival curves. Univariate and multivariate Cox proportional hazards regression

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models were used to calculate hazard ratios (HR) and 95% confidence intervals (CI). Multivariate analyses were performed using a stepwise forward regression model in which each variable with $p<0.1$ or less on univariate analysis was entered into the model. To avoid collinearity, oxygen saturation variables were introduced separately. P values are 2-sided and $p< 0.05$ was considered statistically significant.

Results:

One hundred and four patients were included in the study. Eighty two (78.8%) were males. Mean age was 63.8 ± 11.5 years. Mean FEV1% was 45.6% ± 19.9. Sixty five patients (62.5%) had FEV1 < 50%. Basal SaO_2 was < 90% in 25 cases (24%) and < 85% in 7 (6.7%). Patients were followed up for 590 ± 472 days after the 6MWT. Eleven patients (10.6%) died during the follow-up. Median dyspnea and leg fatigue score after the test were, respectively: 4.5 (2-6) and 1.5 (0-4). Table 1 shows differences between survivors and non-survivors. Patients who died had more dyspnea after the 6MWT, lower basal SaO_2, worse oxygen saturation parameters during the 6MWT, and walked less distance. Table 2 shows correlation between 6MWT distance and 6MWORK and different variables. For most variables, correlation with 6MWT was somewhat better than with 6MWORK. Table 3 shows areas under the ROC curves for the different parameters studied. Only distance walked, basal SaO_2 and dyspnea after the 6MWT achieved an adequate (e.g. larger than 0.8) area under the curve. Pairwise comparison of areas under the ROC curves for these variables did not show significant differences between them (data not shown). Also, area under the curve for 6MWORK was not significantly different than for 6MWT distance (difference: 0.030, 95%CI: -0.054 to

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0.121, p = 0.448). Better combination of sensitivity and specificity for distance walked was found at a cut-off value of 395 m. For basal SaO_2, the best cut-off point was 86%. For Dyspnea, the more useful value of the Borg scale was 7 (table 4). Figure 1 to 3 show Kaplan-Meier survival curves for cases below and above these values, which were significantly different for all variables (distance walked: $p < 0.001$; basal SaO2: p = 0.002; dyspnea: $p < 0.001$). Table 5 shows the results of univariate and multivariate Cox proportional hazards analysis of the relation between clinical variables and all-cause mortality. On multivariate analysis, only 6MWT distance and dyspnea after the test measured with the Borg scale correlated independently with mortality.

Discussion:

The main results of the present study are the following: (1) 6MWORK was not better than distance walked to predict mortality; (2) Both distance walked and dyspnea after the 6MWT correlated with mortality (3) Desaturation during 6MWT did not provide additional prognostic information.

Carter et al found, through ROC analysis, that 6MWORK had better combination of sensitivity and specificity that distance walked to discriminate between low versus high exercise work capacity in COPD patients.[7] Exercise capacity is an important predictive factor of outcome in COPD,[1,11] thus it would be expected that 6MWORK predicted mortality better than distance. On the contrary, the present study found a lower area under the ROC curve for 6MWORK than for distance walked, although the differences did not reach significance. Differences in study populations might account for this discrepancy. Of note, leg fatigue scores in the study by Carter et

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al were greater than those of dyspnea, suggesting that leg fatigue contributed significantly to exercise limitation in their patients.[7] By contrast, the present study found greater dyspnea scores. It is also worth mentioning that, in the study by Carter et al, 6MWORK correlated better with pulmonary function indices and gas exchange variables than 6MWT distance,[7] while we found the opposite results.

Measurement of oxygen saturation during the 6MWT is not a standardized procedure. The current guidelines consider oximetry during the test an optional measurement.[6] In the present study, oxygen desaturation during the 6MWT correlated with mortality. However, in the multivariate analysis it did not remain as an independent prognostic predictor. These results agree with the study of Casanova et al,[4] despite using a different methodology. Casanova et al excluded from the analysis of oxygen desaturation during the test to those patients with resting $SaO_2 < 90\%$ on room air. By contrast, we did not exclude such cases from our analysis, although we added oxygen while performing the test to those patients who were already on long term oxygen therapy. Taken together, the results from the study by Casanova et al and those from the present study suggest that the prognostic information provided by oximetry during the 6MWT is modest at best. Therefore, the results of our study do not support the need to perform oximetry systematically during the test. Takigawa et al,[5] in contrast, found that oxygen desaturation was an independent predictor of mortality. They found no correlation between oxygen desaturation and 6MWT distance. In our study, there was a significant correlation between oximetry parameters and 6MWT distance. This might explain why oxygen saturation was rejected as an independent predictor of mortality in the multivariate analysis.

It is interesting that dyspnea after the 6MWT correlated independently with mortality, and exhibited the larger area under the ROC curve of all the variables studied.

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It is known that dyspnea is an important predictor of mortality in COPD.[12] Dyspnea during activities of daily living, measured with the modified Medical Research Council (MMRC) dyspnea scale, is an essential component of the BODE index which is, in turn, a powerful predictor of prognosis in this disease.[1] Due to the limitations in design of our study, we did not know the values of the score on the MMRC scale for all the patients. Thus, we cannot assess if dyspnea after the 6MWT offers additional prognostic information compared with the more commonly used MMRC scale. However, previous studies have found correlation between dyspnea during daily living measured with the MMRC scale and dyspnea after the 6MWT using the Borg scale.[13] In that study, the MMRC scores correlated better than Borg scores with changes in the inspiratory capacity (used as a marker of dynamic hyperinflation).

The present study has several limitations, the most obvious being its retrospective design, and relatively small sample size. We did not include a random sample from patients along all the spectrum of disease severity, thus the study is vulnerable to selection bias. Actually, the 6MWT is usually performed in patients with more severe disease. Mean FEV_1 was 45%, indicating that our cases had indeed advanced disease. The design of the study did not allow us to evaluate other predictors of mortality in COPD, like the BODE index, although this was not the main objective of the study. Also, few women were included in the study, so we cannot exclude the possibility of gender differences in the prognostic value of any variable.

In summary, 6MWORK was not more useful than 6MWT distance to predict mortality. The present study confirms that 6MWT distance and dyspnea on exertion are key elements in prognostic evaluation in COPD, while the value of exercise oxygen desaturation is less clear. Whether dyspnea after exercise, measured with the Borg scale, offers better prognostic information than other variables in COPD merits further evaluation.

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Figures:

Figure 1: Kaplan-Meier survival curves for patients who walked more (solid line) and less (dashed line) of 395 m. on 6MWT.

Figure 2: Kaplan-Meier survival curves for patients with basal SaO_2 higher (dashed line) and lower (solid line) than 86%.

Figure 3: Kaplan-Meier survival curves for patients with dyspnea scores on Borg scale lower (dashed line) and higher (solid line) than 7.

Table 1: Differences between survivors and non-survivors.

Parameter	Non survivors (n=11)	Survivors (n=93)	p
Males	8 (72.7%)	74 (79.5%)	0.89
Age (yr.)	66.3 ± 9.8	63.4 ± 11.7	0.39
FEV_1%	29.0 (26.0 - 60.0)	42.0 (30.0 - 61.0)	0.32
BMI (Kg/m^2)	26.7 ± 2.6	27.3 ± 4.7	0.64
Basal dyspnea (Borg scale)	0.0 (0.0 - 2.5)	0.0 (0.0 - 0.0)	0.58
Dyspnea after 6MWT (Borg scale)	8.5 (6.5 - 10.0)	4.0 (2.0 – 6.0)	< 0.001
Fatigue after 6MWT (Borg scale)	1.5 (0.0 - 2.5)	1.5 (0.0 -4 .0)	0.87
Basal SaO2 (%)	85.0 (80.5 - 91.7)	93.0 (90.0 - 95.0)	0.001
Mean SaO2 during 6MWT (%)	74.0 (66.0 - 89.6)	86.6 (82.1 - 91.3)	0.015
Lowest SaO2 during 6MWT (%)	70.0 (54.5 - 79.2)	83.0 (74.0 - 88.0)	0.004
CT90 during 6MWT (%)	98.4 (57.7 - 100)	81.6 (9.8 - 93.8)	0.025
6MWT distance (m.)	255.0 (192.5 - 393.5)	480.0 (373.7 - 540.0)	0.0013
6MWORK	21281.0 ± 10058.3	33419.5 ±12486.8	0.002

Results are expressed as number of cases (percentages), mean ± SD, or as median (interquartile range). BMI: body mass index, 6MWT: six-minute walk test, CT90: cumulative percentages of time at saturation below 90%, 6MWORK: work during the 6MWT.

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Table 2: correlation between 6MWT distance and 6MWORK and several variables

	6MWT distance		6MWORK	
	R (95% CI)	P	R (95% CI)	P
CT90 during 6MWT	-0.28 (-0.45, -0.10)	0.0036	-0.18 (-0.36,0.01)	0.054
Mean SaO2 during 6MWT	0.34 (0.16, 0.50)	0.0005	0.24 (0.05, 0.42)	0.013
Lowest SaO2 during 6MWT	0.37 (0.19, 0.53)	0.0001	0.30 (0.11, 0.47)	0.0026
FEV1	0.33 (0.15, 0.49)	0.0009	0.39 (0.21, 0.55)	< 0.001
age	-0.37 (-0.52, -0.19)	0.0002	-0.23 (-0.40, -0.04)	0.018
BMI	-0.02 (-0.21, 0.17)	0.8058	…	..
Dyspnea after 6MWT(Borg scale)	-0.32 (-0.49, -0.13)	0.0015	-0.29 (-0.46, -0.10)	0.003
Fatigue after 6MTW (Borg scale)	-0.009 (-0.20, 0.19)	0.9295	-0.14 (-0.33, 0.05)	0.152

For definitions, see legend to table 1.

Table 3: Area under the ROC curve for different variables

	AUC	95% CI
6MWT distance (m.)	0.80	0.71 to 0.87
6MWORK	0.77	0.68 to 0.85
Basal SaO2	0.80	0.71 to 0.87
CT90 during 6MWT	0.71	0.61 to 0.79
Mean SaO2 during 6MWT	0.73	0.64 to 0.81
Lowest SaO2 during 6MWT	0.78	0.69 to 0.86
FEV1 %	0.61	0.51 to 0.71
Age	0.53	0.43 to 0.63
BMI	0.54	0.44 to 0.64
Dyspnea after 6MWT (Borg scale)	0.88	0.80 to 0.94

CI: confidence interval. For further definitions see legend to table 1

Table 4: values with the best combination of sensitivity and specificity on ROC analysis.

Variable	Cut-off value	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value	Negative predictive value
6MWT distance (m.)	395	81.8 (48.2-97.2)	72.04 (61.8-80.9	25.7	97.1
Basal SaO_2 (%)	86%	63.6 (30.9-88.8)	90.3 (82.4-95.5)	43.7	95.5
Dyspnea after 6MWT (Borg scale)	7	75.0 (35.0-96.1)	92.2 (84.6-96.8)	46.2	97.6

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Table 5: Results of univariate and multivariate Cox proportional hazards analysis of the relation between clinical variables and all-cause mortality.

	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
6MWT distance	0.994 (0.991,0.998)	0.003	0.994 (0.990, 0.998) …	0.005 …
CT90 during 6MWT	1,009 (0.989, 1.030)	0.350	…	…
Mean SaO2 during 6MWT	0.939 (0.891, 0.989)	0.019	…	…
Basal SaO2	0.910 (0.856, 0.967)	0.002		
Lowest SaO2 during 6MWT	0.963 (0.932, 0.997)	0.033	…	…
FEV1	0.987 (0.949, 1.026)	0.520	…	…
Dyspnea after 6MWT	1.553 (1.138, 2.119)	0.001	1.553 (1.138, 2.120)	0.005

HR: hazard ratio, CI: confidence interval. For further definitions see legend to table 1. Ellipses denote variables not included in the final model.

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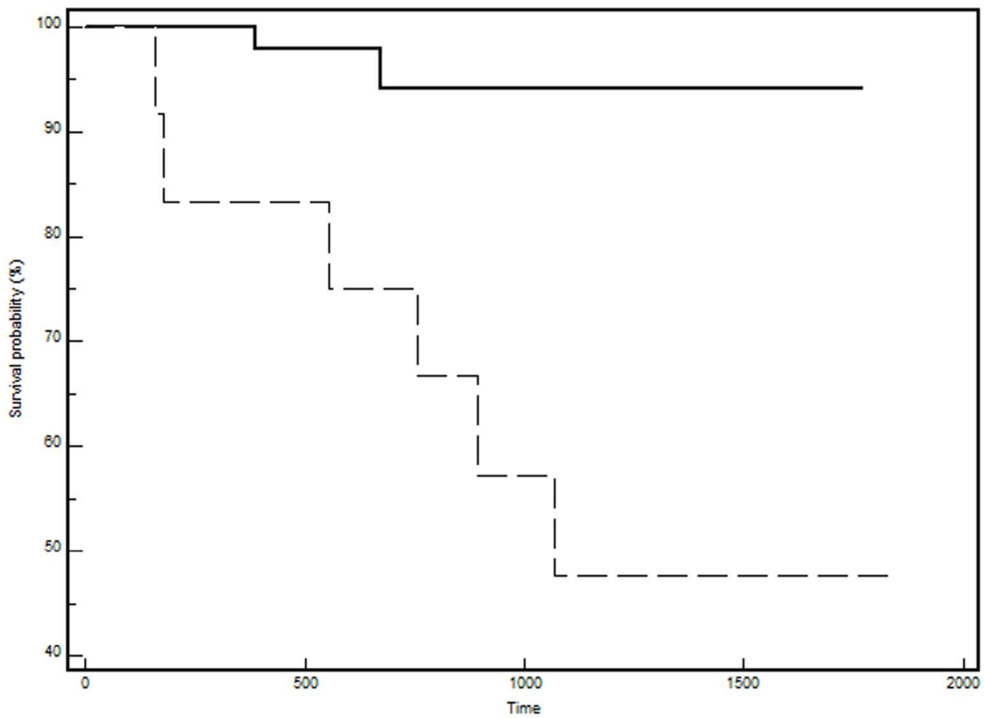

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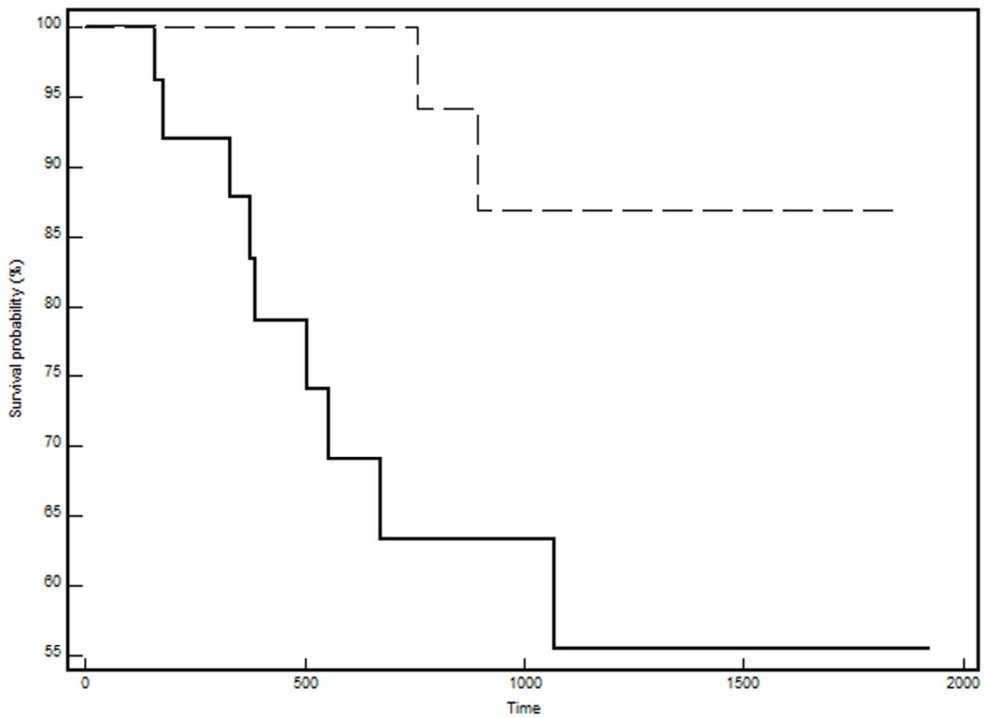

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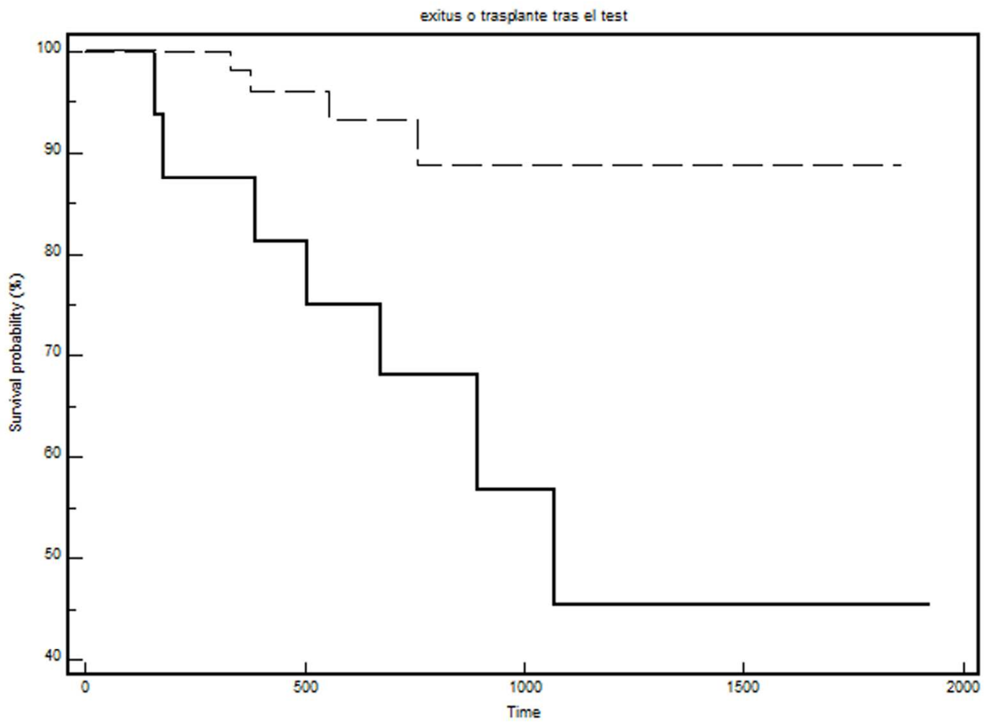

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