

SURVIVAL TIME IN CYSTINOSIS. A COLLABORATIVE STUDY

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Summary

In a retrospective study the overall survival time of 205 cystinotic patients of six countries was determined. The median survival time was 8.5 years. The median time for 'renal death' (age at death due to uraemia or age at starting renal replacement therapy) was 9.2 years. The youngest patient dying of renal death was 5.2 years. No sex difference in survival time was noticed. Furthermore no difference in survival time was noted between the different countries.

The analysis of the overall survival curve indicates no clear differences between the infantile and adolescent types of cystinosis.

Introduction

Patients suffering from the infantile or the adolescent type of cystinosis develop terminal renal failure. In a retrospective study the following data of 205 patients having cystinosis were evaluated in a survival analysis: date of birth, date of death, date of start of renal replacement therapy and date of the last observation. The data were collected from 33 hospitals in Britain (n=41), France (n=46), West Germany (n=95), Portugal (n=1), Spain (n=18) and Switzerland (n=4).

Methods

For the analysis the program PIL of BMDP was used [1], which allows evaluation of data from patients still alive or lost to follow-up (so-called incomplete or censored data). The product limit method was used for estimating the survival distribution. The equality of survival curves was tested applying both

Mantel-Cox and Breslow statistics. These tests differ in the way the observations are weighted. In contrast to the Mantel-Cox test the Breslow test gives greater weight to early observations and is less sensitive to late events which occur when few patients on the study remain alive [1].

Results

The median survival time for all patients (n=205) suffering from cystinosis was 8.5 years (75th percentile = quartile (Q₁): 7.3 years; 25th percentile = quartile (Q₃): 10.6 years) (Figure 1). In this analysis the age at death due to uraemia or the age at starting renal replacement therapy was regarded as age at renal death. Fifteen patients died of electrolyte imbalance, 43 of uraemia and 16 of unknown reasons. Fifty-nine children started haemodialysis and four were primarily transplanted. Fifty-four patients were still alive and 14 were lost to follow-up. The survival curve exhibits at least two different components: a linear fall due to non-renal deaths, e.g. electrolyte imbalance, and an exponential fall caused by 'renal deaths'. The sex ratio in our study was male:female 115:90. No sex difference in survival time was noted (p values: Breslow 0.921; Mantel-Cox 0.7292 (Figure 2). In the male patient the median survival time was 8.6 years (Q₁ 7.0 years; Q₃ 10.6 years), in the female patients 8.5 years (Q₁ 7.3 years; Q₃ 10.6 years). Furthermore no difference in survival time was noticed between the different countries (p values: Breslow 0.4571; Mantel-Cox 0.9060) (Figure 3). The patients of Switzerland and West Germany as well as Spain and Portugal were grouped together because of the small number.

The youngest patient dying of 'renal death' was aged 5.2 years. When taking only the data of the patients dying of 'renal death' into account and when regarding losses due to electrolyte imbalance as censored data, the median survival time was 9.2 years (Q₁ : 8.1 years; Q₃ : 11.2 years). The survival curve (Figure 4) exhibits only the exponential fall already noted in Figure 1. In these data a sex difference could not be demonstrated (p values: Breslow 0.3884; Mantel-Cox 0.8959). Concerning 'renal death', no difference in survival time was noticed between the different countries (p values: Breslow 0.2267; Mantel-Cox 0.1760).

Discussion

In our study the survival time of patients with infantile and adolescent types of cystinosis was analysed. No plateau formation was noted at the right-hand end of the survival curve indicating no clear cut difference between infantile and adolescent cystinosis. Therefore survival time does not differentiate between these two types of cystinosis. No clear cut difference in survival time in the patients of the different countries could be seen. The low p value of the Breslow test indicates a non-significant difference at the beginning of the survival curve (Figure 3). This non-significant difference may be caused by a selection bias, due to different numbers of deaths caused by electrolyte and water imbalances. The low p value in the Mantel-Cox test of 0.1760 for the risk of dying from

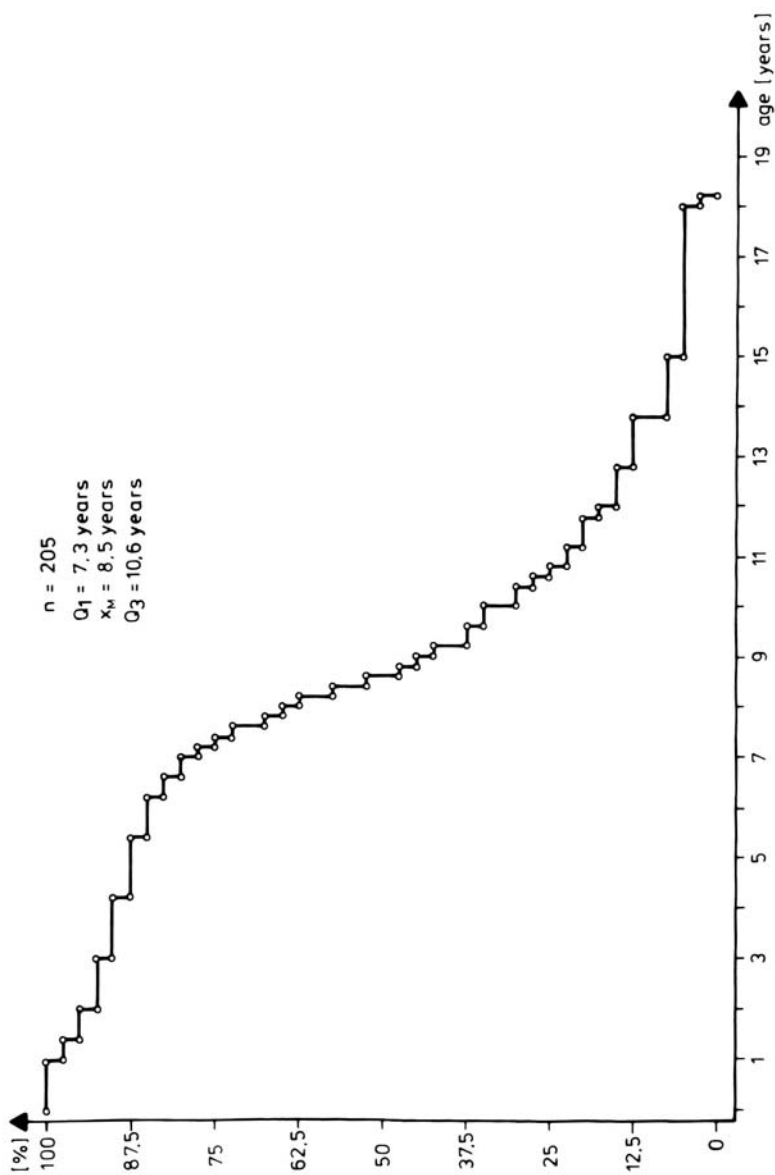


Figure 1. Overall survival of cystinotic patients

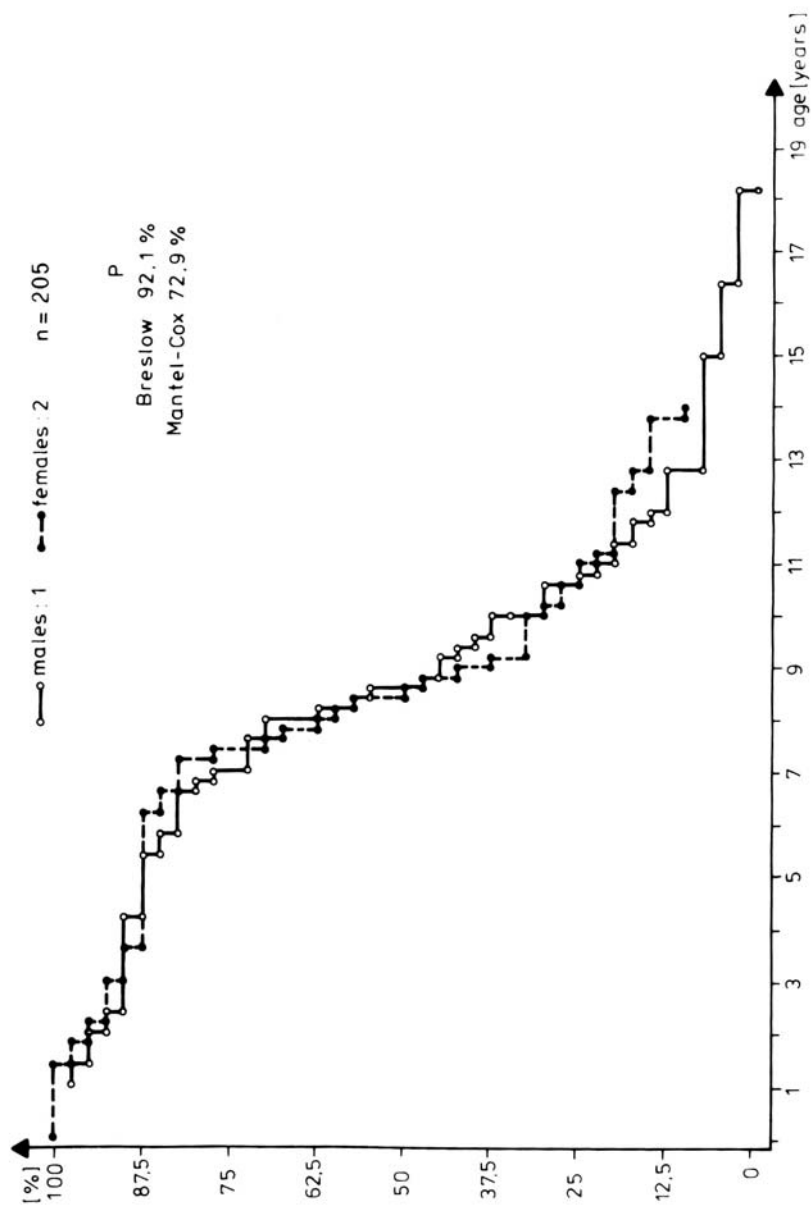


Figure 2. Overall survival of males and females with cystinosis

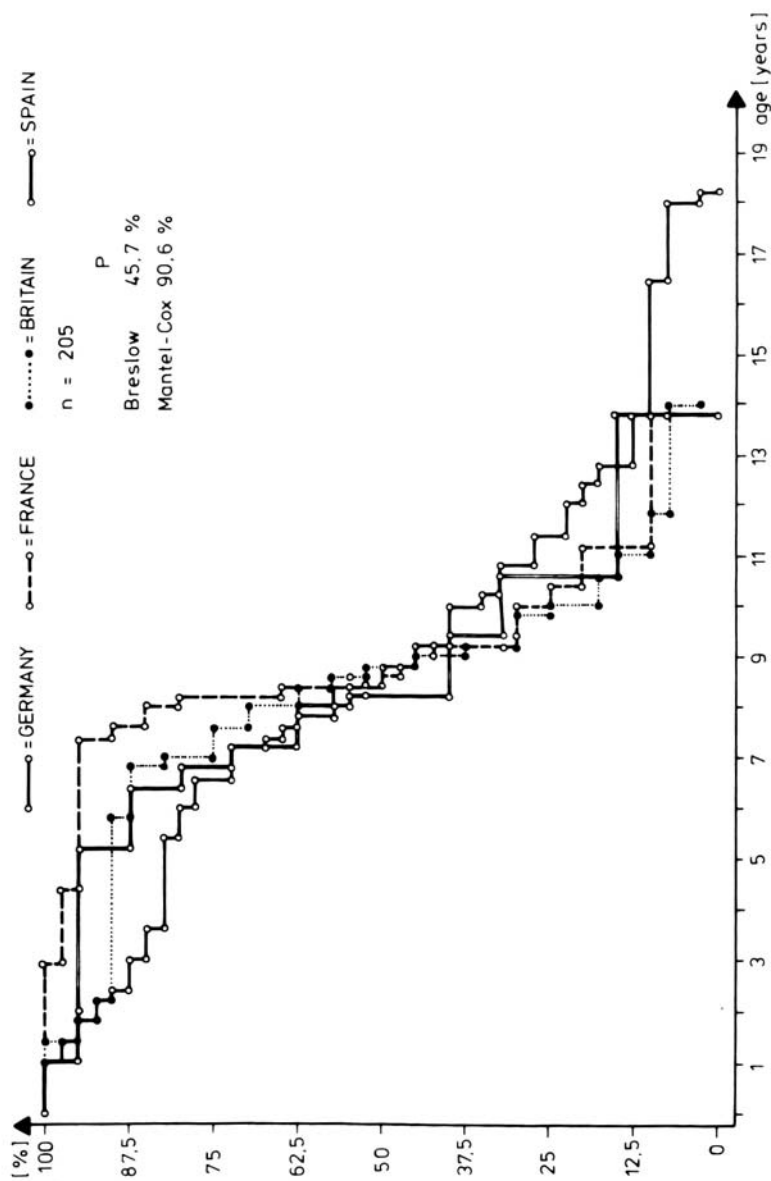


Figure 3. Overall survival of cystinotic patients of four countries

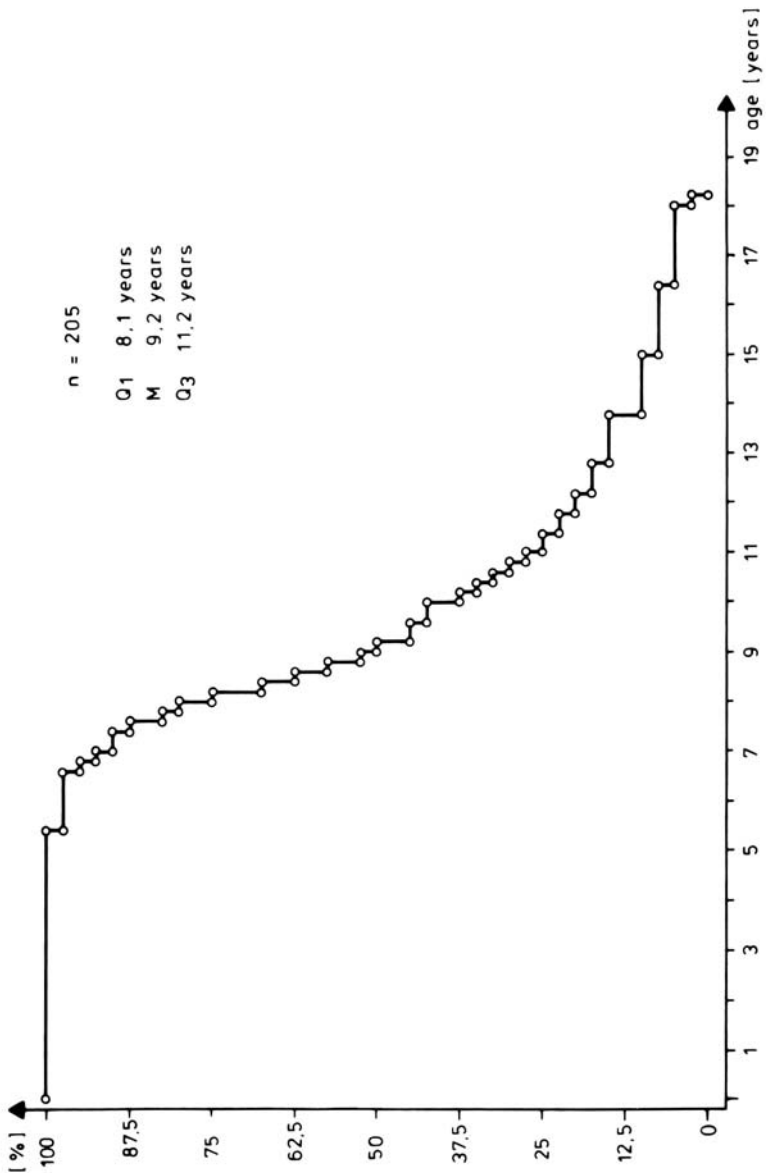


Figure 4. Survival of cystinotic patients suffering from renal death

uraemia in the different countries is probably due to a selection bias.

Our results concerning the risk of dying from uraemia are in agreement with the data reported by EDTA [2]. This is not surprising, as most of the patients registered in the report of EDTA are included in our study. In contrast to the EDTA data our data demonstrate an overall survival time in patients with cystinosis. Furthermore the risk of coming to end stage renal disease is assessed.

References

- 1 Dixon WJ. *BMDP Statistical Software 1981*. Berkley: University of California Press
- 2 Donckerwolcke RA, Broyer M, Brunner FP et al. *Proc EDTA 1981*; 18: 49

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Open Discussion

BARNES (Birmingham) I was not quite sure how much effect of the therapy with either dialysis or transplantation was shown in your survival curves. Were these just patients who received no treatment with dialysis or transplantation or were they included?

GRETZ These are only patients without haemodialysis or transplantation, the study ended at the point where this treatment is started.

BARNES Have you any data on the effectiveness of dialysis or transplantation in this series?

GRETZ No, it was the aim of the study to assess the 'natural' course of the disease.

BROYER (Paris) I could answer the question, because last year we studied the survival after transplantation in cystinotic patients and we found a significantly better result in cystinotic patients in comparison with other children with other primary renal diseases, at least a 20 per cent better survival rate after transplantation.

SCHÄRER (Heidelberg) One should underline that this was a study done in paediatric centres only. It may well be that in other centres there are adult patients with cystinosis; in fact a few years ago when we looked at the EDTA registry data we found that more adult patients died from cystinosis than children. I wonder if Dr Gretz has any idea if there are data available on survival rates of adults?

GRETZ We have some information that there are patients older than 40 years coming to end stage renal disease due to cystinosis. This is really surprising as in general it is thought that cystinosis is a problem of paediatrics.

BARNES I should like to support the last but one speaker. The results of transplantation on cystinotic children in our hands are certainly as good, if not better, than the treatment of any other paediatric causes of renal failure.

CALLIS (Barcelona) Have you observed different types of survival time in patients belonging to the same family?

GRETZ When we looked at the data of some families we saw that these families had exactly the same rate of progression of chronic renal failure and exactly the same survival time. These data of siblings are useful to assess the effect of treatment.

WILL (Leeds) Could you comment on the fact that the curves from the different countries overlapped exactly at the median point. Can you give some kind of mathematical interpretation of that, if it has some significance? Could you comment on whether this kind of modelling is likely to be useful for other well defined conditions?

GRETZ The problem is that we have data from different countries. This means that we have selection bias especially in the first five years where the curves do not overlap. The curves meet at the median point because of the same underlying renal diseases.

This method should be used especially in genetic disorders. It is very useful to assess the natural course of the disease and to look for influencing factors; then it can also be applied to calculate group-specific progression rates.