

DISSECTING THE CENTRE EFFECT

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Summary

In 3,653 first cadaveric transplants performed in 30 centres in the United Kingdom and Ireland between 1978 and 1983, 40 pre- and peri-operative factors were analysed. Nine were associated with significant changes in the risk of graft failure, including age, sensitization, HLA-B matching, number of renal arteries and patches, dialysis duration, anoxia time, ischaemia time, year and centre. The analysis allowed joint estimation of each factor's influence. The effect of the 'centre' factor on graft survival was 'independent' of all other factors suggesting that it did not originate from the pre- and peri-operative events analysed.

Introduction

The centre at which a transplant is performed in the United Kingdom (UK) and Ireland is one of the major factors affecting graft outcome [1-4]. The most recent approach was to define the effect not only in terms of the reason for failure (e.g. rejection, technical failure or death), but also in terms of the post-operative time zone in which the terminal event occurred [3].

Based upon this analysis, the British Transplantation Society conducted a detailed audit of selected centres. They gained the impression that one of the major causal factors was the employment of pre-operative blood transfusions [4], an observation consistent with previous studies [2].

Our investigation extended the investigations in another direction by testing the contribution to the centre effect of factors shown by multifactorial analysis to significantly influence graft failure [5,6].

Methods

The database and the statistical methods are described elsewhere [5-7]. The data, collected through paper forms filled in at various stages during the natural

history of the transplant, consisted of pre- and peri-operative details of 3,653 first cadaveric transplants from which diabetic patients and under 15-year olds had been excluded. The transplants were performed between 1978 and 1983 in 30 centres throughout the UK and Ireland. In the results, the identity of each centre has been deliberately obscured. For the analysis of the 'calendar period of transplantation' factor the database was extended to include the 1984 data, and the study period was curtailed at 100 days post-transplant.

The statistical method is a form of multiple regression for survival which allows the risk (or hazard) of graft failure to be estimated having taken account of a number of transplant factors. The various factors identified as having a significant effect on graft outcome are discussed in detail in Gilks et al [6] and they include transplant 'centre'. It is recognized that centre represents a mosaic of factors, each of which may have a different influence in different places.

The risk of graft failure associated with a factor is expressed as a ratio. For example, the risk of graft failure for patients aged greater than 45 years is expressed relative to the risk associated with a *baseline* age category (age 15–29). This relative risk is estimated as for patients who otherwise have the same set of clinical characteristics; that is the multifactorial approach gives the effect of age over and above the joint effects of other influential factors.

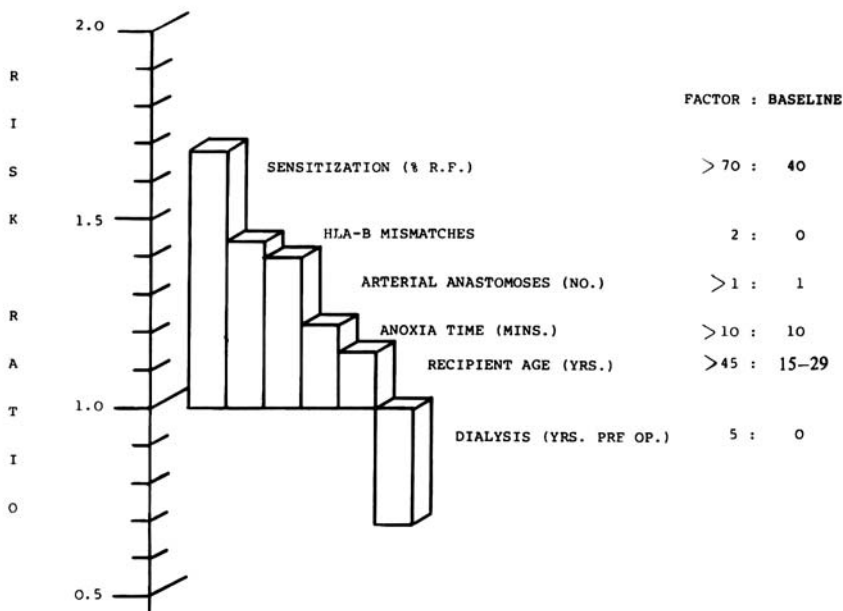


Figure 1. Summary of factors found to be associated with a significant increase (above unity) or decrease (below unity) in the relative risk of graft failure (vertical axis). The factor is listed on the right together with the chosen baseline which is represented by the horizontal axis

The effect of each factor is qualified by its standard error and its statistical significance which have been omitted for brevity. Only factors significant at the five per cent level are presented here [5,7]. The graphical presentation of the relative risk is described in the legend to Figure 1.

Results

Of 40 separate recipient, donor, matching and surgical factors eight were found to have an important effect on graft survival. Several factors were poorly recorded and therefore unusable and one was excluded because it may have been spuriously recorded, namely the warm time. Blood transfusion was difficult to analyse because of the problems in identifying a non-transfused group and because of inaccuracies in the recording of the number of transfusions given. The effect of six of the eight variables is illustrated in Figure 1. They include high sensitization, HLA-B mismatching, the (imputed) number of arterial anastomoses, the anoxia time (i.e. the interval between cessation of donor ventilation and circulatory arrest), recipient age and the duration of chronic haemodialysis prior to transplantation. With the exception of dialysis duration all factors were associated with an increase in the relative risk of graft failure. By contrast dialysis was associated with a reduced risk of graft failure and this effect was incremented for each additional year of dialysis up to five (the limit of the study).

The centre effect is shown in Figure 2. The two sets of histograms show the persistence of the centre effect despite the aforementioned factors. The first set labelled 'before' is the centre data prior to multifactorial analysis. In the histogram set labelled 'after' the independent effect of centre is illustrated. The small changes in the middle ranking centres are attributed to randomness. These two histogram sets illustrate the persistence of the centre effect after accounting for all pre- and peri-operative risk factors.

The year in which the transplant was performed will determine the outcome of the graft [6]. In Figure 3 time is divided into two consecutive periods and the centre rank is contrasted for each. Some centres change rank, indicating an increase or a decrease in the graft failure risk between the two periods; others remain the same indicating a consistent relative risk.

Discussion

The results emanating from any two centres are seldom identical. Randomness, real superiority and inferiority and the number of transplants performed per centre all contribute to this difference. Amongst the variety of salient events which might have been chosen to compare centres the rate of graft failure was considered the most sensitive.

The post-operative time interval over which the analysis ranges has a large influence on the rank order of centres [3]. This may be attributed either to changes in the patients' clinical management between periods, for example when the recipient transfers from in-patient to out-patient, or to different aetiological processes of rejection, each of which requires a unique therapeutic strategy.

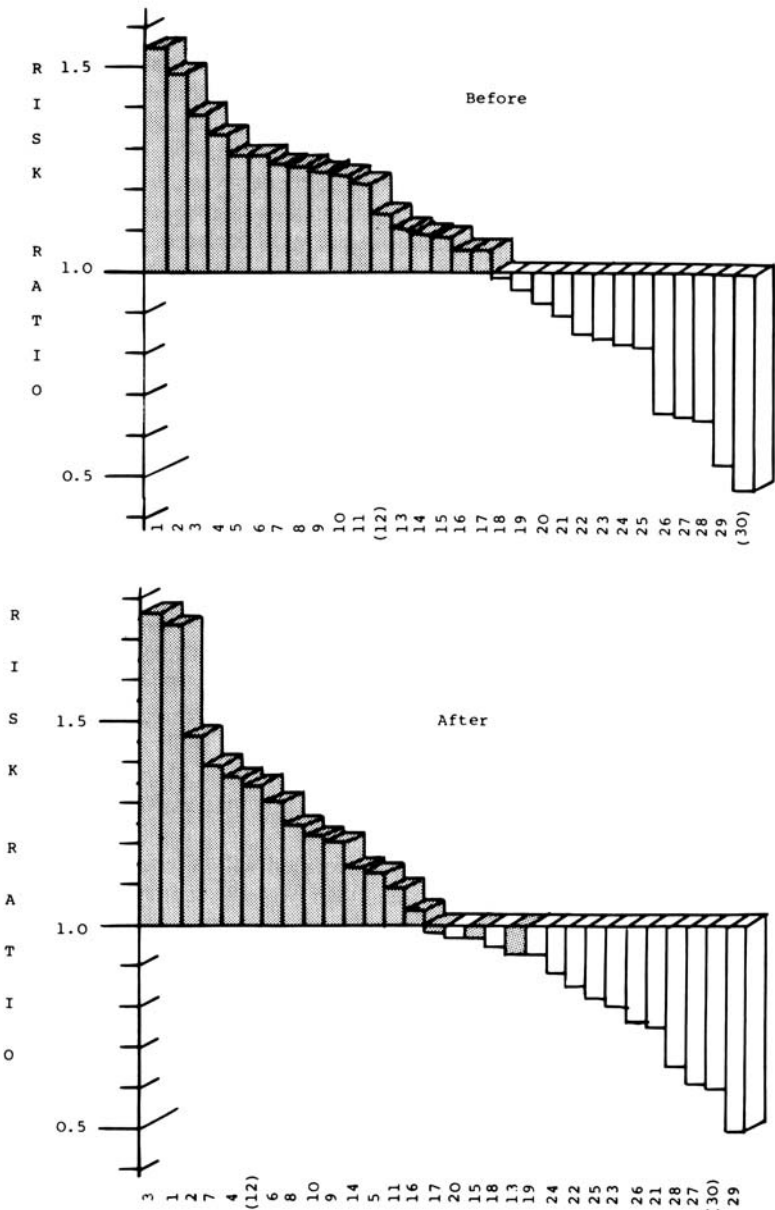


Figure 2. Comparison of results of 30 centres; the relative risk of graft failure for each centre is expressed in relation to the average for all centres. Centres are displayed in rank order in each histogram and labelled with a number. The histogram series labelled 'before' is the spread of centre results before multifactorial analysis. The histogram series labelled 'after' is the centre effect persisting after the factors listed in Figure 1 have been accounted for jointly. Note the lack of change in the rank order. Brackets refer to centres with fewer than 10 graft failures during the study period

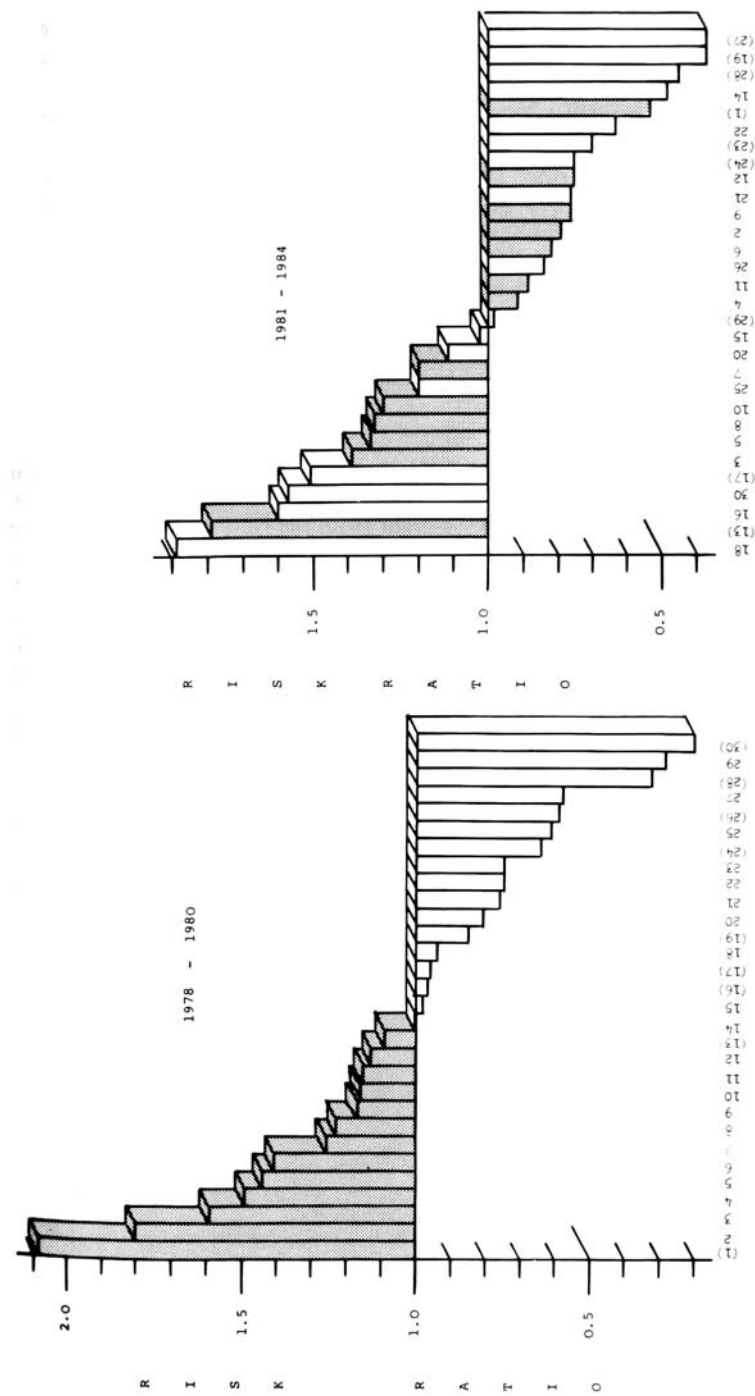


Figure 3. Comparison of the results of 30 centres; the relative risk of graft failure for each centre is expressed in relation to the average for all centres during two consecutive periods. Centres are numbered in rank order in each histogram; the centre labels differ from those in Figure 2. Note the change in the rank order of some centres and the lack of change in others. Brackets refer to centres with fewer than 10 graft failures during the study period

The multifactorial methods advocated take account of correlations between factors when estimating their effects on graft survival [5-7]. They differ from the unifactorial methods in common use which cannot readily draw distinctions between the effect of centre and the effect of other influential factors such as age, sensitization and HLA-B matching. The 'independence' of centre from pre- and peri-operative factors points to unknown post-operative events which influence the therapeutic environment in which the patient and his transplants are treated. These will be the subject of further intensive investigations.

One of the deficiencies in this study is the lack of available detail on two factors which were thought to have influenced the centre effect, namely pre-operative blood transfusions and post-operative steroid dosage [2,4]. Computer storage of this information will assist such analyses in the future.

Acknowledgments

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