

INVITED COMMENTARY

The center effect in kidney transplantation

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A “center effect,” variability in outcome unrelated to case mix or chance, is a recognized determinant of outcome in kidney transplantation. Since earliest investigation, center size (volume) has been its primary surrogate. Transplantation has matured, and outcomes have progressively and uniformly improved, narrowing short-term differences between centers. Does the center effect still exist? And if so, what is its nature, beyond usual donor, transplant organ and recipient characteristics, which has been elusive?

Investigation of the center effect has been retrospective and registry-based, making it victim to the inherent limitations of registries and their data.

The first description of a center effect was in a report of the Human Renal Transplant Registry in 1973 [1]. While the Registry was international, with voluntary participation from 246 institutions primarily in the United States, Europe, Australia and Canada, only the experience of the 100 reporting U.S. centers was analyzed in relation to center size. In those centers performing fewer than 25 transplants per year, patient mortality at one year did not change over the years from 1968 to 1971, 29 to 27%, whereas in centers performing more than 25 transplants per year patient mortality decreased from 29 to 17%. Of note, graft survival did not improve over the four-year interval. (The decline in mortality may have represented the beginning of the primary lesson of the 1970s—save the patient not the kidney—enabled by essentially universal availability of dialysis funded by

U.S. public medical insurance.) A prior report of the Registry in 1968 had shown no difference in one-year graft survival in comparison of experienced (having performed at least 30 transplants prior to 1966) versus lesser experienced centers [2].

Recognizing that center performance would be scrutinized with the advent of public medical insurance payment for treatment of end-stage kidney disease in the United States, Opelz, Mickey, and Terasaki analyzed the outcome of first transplants recorded in the UCLA voluntary registry of both deceased-donor (95 centers) transplantation and living-donor (84 centers) transplantation [3]. The transplants were performed over a five-year period, 1969 to 1973. While the range of survival was very wide, there was no relationship between center size (a minimum of two transplants performed during the five-year study period) and one-year graft survival in either deceased-donor or living-donor transplantation. The authors concluded that “other factors beside size of centers are probably of greater importance in influencing transplant survival rates.”

In the latter half of 1982, on behalf of the British Transplantation Society, a team consisting of a transplant surgeon, a nephrologist and an immunologist, audited eight (of a total of 29) kidney transplant centers in the UK and Ireland, four with high and four with low three-month graft survival [4]. Each center’s last 50 consecutive first deceased-donor kidney transplants prior to the end of 1981, with follow-up through

1982, were analyzed. At one year, across the centers the range of patient survival was 82 to 98% and graft survival 54 to 82%. Variations in the incidence of irreversible acute rejection and death with a functioning graft were the primary reasons for the differences across centers. The authors “were also impressed by the importance of careful and well-organized clinical management, although it is impossible to subject this to statistical analysis.”

Over the next two decades, repeated study of the voluntary UCLA and mandatory UNOS registry databases showed the persistence of a center effect, measured by one-year graft survival, primarily in deceased-donor transplantation. Twenty-five to 30% of the variation was attributed to center effect [5]. Part of the variability in the 1980s was attributed to the learning curve of use of cyclosporine, newly introduced [6], and pretransplant red blood cell transfusions and cold ischemia time [7]. An analysis of first deceased-donor transplants done from late 1987 through 1991, in which the difference in one-year graft survival between high and low performing centers was ~20 percentage points, showed that half the center effect was associated with events during the transplant hospitalization—there was less primary nonfunction and delayed graft function, and better survival of grafts with early dysfunction or early rejection, in the better performing centers [8]. While earlier study had shown no center effect in living-donor transplantation [9], an effect associated with center size, albeit lesser due to the better outcomes of living-donor transplantation, was evident in an analysis of transplants performed from 1996 to 2001 [10]. All centers which performed over 400 living-donor transplants during the study period had one-year graft survival rates above average, whereas centers which performed 100 or less showed a wide range, 87–100%. Meanwhile, another analysis of all transplants, both living donor and deceased donor, performed from 1988 to 1994, showed an association of lesser patient and graft survival at one and three years with smaller center size (fewer than 25 transplants per year) [11].

In part to examine the effect of the public release of transplant center-specific reports by the Scientific Registry of Transplant Recipients on center outcome, an analysis of all U.S. kidney transplants performed from 1996 through late 2009 showed no effect on the range of three-year patient and graft survival after the introduction of the reporting in 2001 [12]. The center effect was unchanged, with 33% of deaths and 29% of graft failures at three years attributed to it [5].

A recent systematic review of 24 studies of the center effect in transplants performed primarily before year 2000 across five continents, with the goal of identifying characteristics that may be associated with outcome, showed no specific associative characteristic, including center size [13]. A subsequent registry study by the same investigators, of all transplants performed from year 2000 through 2013 at five centers in Ontario, Canada, showed the persistence of a center effect in this recent cohort, as measured by death-censored graft loss (HR 0.72 to 1.22), and a trend to lesser risk of graft loss but not mortality in higher volume centers, at a median follow-up of over five years [14].

The aim of the retrospective ANZDATA Registry study in this issue [15] was to evaluate the association of patient and center factors with kidney transplant outcomes in a contemporary cohort (transplants performed from 2004 through 2014) of first kidney transplant recipients in 17 Australia and New Zealand centers. The center characteristics studied were (i) center size, (ii) percentage of patients transplanted and followed up in the same center, and (iii) the average ischemic time for deceased-donor transplants in a center. The range of five-year patient survival was 81 to 94% and graft survival 72 to 88% in deceased-donor transplantation, and 90 to 100% and 79 to 97%, respectively, in living-donor transplantation. Center effect accounted for 41% of the variation in mortality and 55% of the variation in graft loss in deceased-donor transplantation but none of the variation in living-donor transplantation. Centers with an average total ischemic time greater than 14 h for deceased-donor transplant showed a higher risk of mortality in both deceased-donor transplantation (HR 2.24) and living-donor transplantation (HR 1.76). There were no center characteristics associated with delayed graft function, acute rejection, death with a functioning graft, or death-censored graft failure in deceased-donor transplantation. Oddly, in living-donor transplantation, centers with an average total ischemia time less than 12 h for deceased-donor transplant showed a greater risk of death-censored graft failure (HR 1.67). The incidence of delayed graft function in living-donor transplantation was low (3%), but there was a higher risk (HR 2.05) in small centers (less than 35 total transplants per year). There was no center characteristic associated with acute rejection or death with a functioning graft in living-donor transplantation. In contrast with the above earlier study [10], the small centers showed a lower risk of death in living-donor transplantation (HR 0.48). The authors concluded that the contribution of center effect outweighed that of case mix in the variation of outcome

in deceased-donor transplantation. They propose that the novel finding of the association of lower ischemic time in deceased-donor transplant with lesser mortality in both deceased-donor transplantation and living-donor transplantation might represent a modifiable risk factor for center outcomes. They posit that this “center characteristic likely reflects the quality, organization and performance of a transplant team in a center.”

The center effect persists and is evident in longer-term outcome. Its surrogate is not exclusively center size. Its nature has escaped definition due to the limitations of investigation to date. It may remain elusive due to a multitude of intangible or difficult to measure variables, such as center attitudes, behaviors, and organizational structure and function, as discussed in many of the above studies, and an inherent subjectivity.

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