Transplant International

Transplant Trial Watch

THE PETER MORRIS CENTRE FOR EVIDENCE IN TRANSPLANTATION

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To keep the transplantation community informed about recently published level 1 evidence in organ transplantation ESOT (https://esot.org/) and the Centre for Evidence in Transplantation (www.transplantevidence.com) have developed the Transplant Trial Watch. The Transplant Trial Watch is a monthly overview of 10 new randomized controlled trials (RCTs) and systematic reviews. This page of Transplant International offers commentaries on methodological issues and clinical implications on two articles of particular interest from the CET Transplant Trial Watch monthly selection. For all high quality evidence in solid organ transplantation, visit the Transplant Library: www.transplantlibrary.com

Randomized controlled trial 1

Donor wound satisfaction after living-donor liver transplantation in the era of pure laparoscopic donor hepatectomy. Lee, J. M., et al. Surgical Endoscopy 2021; 35(5): 2265-2272.

Aims

This study aimed to assess donor satisfaction following pure laparoscopic living-donor hepatectomy (PLLDH) versus donors who underwent open living-donor hepatectomy.

Interventions

Donors were randomly assigned to receive a donor satisfaction questionnaire during follow-up visits.

Participants

590 living donors who underwent living-donor hepatectomy.

Outcomes

Donors' satisfaction and quality of life.

Follow-up

Not applicable.

CET conclusion

This is an interesting study in live donor liver transplantation. However, patients were not randomized to different surgical techniques. They were randomized to receive a questionnaire about wound satisfaction. The operative incision used actually followed an era approach, with L-shaped incision progressing to upper midline, then laparoscopic-assisted and finally pure laparoscopic donor nephrectomy. The results of the questionnaires cannot therefore be extracted from that era effect and are subject to bias. It was a good-sized study, including a total of 149 patients across 3 groups (inverted-L, upper midline, and pure laparoscopy). The body image and cosmetic scales were significantly better in the pure laparoscopic group. Self-confidence was also significantly higher in the pure laparoscopic group. Importantly, there was no comparison made between the scores reported by patients with pure laparoscopic and laparoscopic-assisted approaches.

Trial registration

Not applicable.

Funding source

No funding received.

Randomized controlled trial 2

Current state of evidence on kidney transplantation: how fragile are the results? Budhiraja P, et al. Transplantation [Online ahead of print].

doi:10.1111/tri.14017

Aims

The review aims to assess the strength of the evidence of randomized controlled trials (RCTs) in kidney transplantation.

Interventions

The study included RCTs reporting on pharmacological, surgical, or educational interventions.

Participants

The review included RCTs in kidney transplantation published over the last 10 years that used 1:1 randomization and reported at least one significant dichotomous outcome.

Outcomes

Fragility index, the number of patients reported lost to follow up, and whether imputation was performed for missing data and subjects who discontinued.

Follow-up

Not applicable.

CET conclusions

The study analyzed the strength of the evidence according to the fragility index as an alternative to p-values of randomized controlled trials (RCTs) in kidney transplantation. Medline was searched to identify RCTs of any type of intervention in kidney transplantation published in ten selected high-impact journals over the last 10 years. The authors did not provide a rationale for their selection of the high-impact journals. RCTs had to use 1:1 randomization and report on at least one significant dichotomous outcome to be included. Two independent reviewers identified 57 studies to be included and extracted the data. Strength of the evidence was assessed using the fragility index, which was defined as the number of additional events required to change significant results to nonsignificant results. Data showed that 53% of the trials had a fragility index of ≤ 3 and 26% a fragility index of 10. Eighty percent of trials reported loss to follow up and 4% used a method of imputation for missing data. The authors suggest that the fragility index may be considered alongside p-values when interpreting data.

Trial registration

Not applicable.

Funding source

No funding received.

Clinical impact summary

This is a really interesting paper that questions the methodology of randomized controlled trials in transplantation. It is a selected population of studies, being from only the top 10 transplant journals and with at least one significant result in the abstract (with $P < 0.05$). However, a good number of trials were included, 57 in total, which may give some insight into this area.

They were all studies with dichotomous outcomes, 1:1 randomization, and without clustering or cross-over (because the fragility index can only be calculated for this specific group of RCTs). Ninety percent of the included RCTs compared drugs, mostly immunosuppression and 80% of the trials were open-label. Seventy-nine percent included intention to treat analysis—although it seems that this was, as we say, "modified intention to treat," to exclude dropouts, as only 4% of the included studies imputed an outcome for missing data.

The authors found that in a large minority of trials (43%), the number of patients lost to follow-up was high enough to potential change the outcome of the study if they had been included.

The mean fragility index (FI) of all included studies was only 3 (this is the number of patients required to change from an event to nonevent to change the outcome of the study). This is lower than the FI previously estimated for RCTs in both medicine and cardiovascular disease (8 and 13, respectively). The number of subjects who discontinued the study due to adverse events was higher than the study fragility index in 61% of included studies.

Twelve percent of included studies had a fragility index of 0! This is possible as the Fisher exact test was used to recalculate (more appropriately) the p-value in small and nonparametric results where Chi-squared had been used.

This paper encourages vigilance when assessing the robustness of significant conclusions from RCTs. It also throws a stark light on the issue of classifying study results into "significant" and "nonsignificant." In this particular area, of immune suppression in

transplantation, any reported "significant" results are very likely to be fragile.

Furthermore, it highlights issues around study design in transplantation; 46% of the studies did not include information on power calculations, and it may be that they were either knowingly or unknowingly underpowered. There is also the question of adequately accounting for dropouts and the imputation of missing results to prevent skewing of outcome data.

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