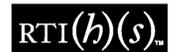




Risk of Selected Outcomes After Solid Organ Transplantation: A Literature Review



RTI HEALTH SOLUTIONS™

Poster # 50

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ABSTRACT

Background: As transplant surgery and immune-suppression therapy have improved, solid organ transplant patients are surviving longer. A summary of literature on risks of selected outcomes is an important initial step to understanding the background rates of selected outcomes in clinical trials of investigational drugs.

Objectives: The objective of this study was to systematically review the risk of selected outcomes after adult solid organ transplantation.

Methods: We searched Medline for epidemiologic studies published from 1998 - April, 2005, on risks of selected outcomes among lung, heart, liver, pancreas, and kidney transplant patients. Selection criteria included: outcome types, N >500 subjects, age ≥18, geographic locations, and study design. Of the scanned 3,776 abstracts, 40 of the epidemiologic studies were selected for detailed review: 11 for malignancy including 4 for post-transplant lymphoproliferative disease (PTLD), 12 for serious infections, 5 for post-transplant diabetes (PTDM), 2 for hypertension, 3 for dyslipidemia, 9 for graft and subject survival.

Results: Two studies reported incidence rates per 100 renal transplant patients per year for all cancer excluding non-melanoma skin to be 0.58 and 0.89. Two studies had similar cumulative incidence of cancer in renal transplant patients (11.8-12.2%; median follow up=12.4-13.4 person-years). Cumulative incidence of PTLD was approximately 1-2% in heart, liver, kidney transplant recipients. Symptomatic cytomegalovirus (CMV) infection occurred in 20-60% of all transplant patients. After renal transplant, incidence of hospitalization for fungal infection was 5.2 admissions per 1,000 person-years. Cumulative incidence of UTIs was reported to be 26%-43% at 1 to 6 months after kidney transplant. Among cardiovascular outcomes, 33-84% of renal transplant patients had prevalent hypertension; 46-64% had elevated cholesterol, and 4.9-6% of patients developed new PTDM in the first year after renal transplant. At one year posttransplant 15-16% of kidney or kidney-pancreas recipients had had allograft failure, and 4%-7% had died.

Conclusions: The range of risk estimates may be attributable to differences in study populations, viral infections, immunosuppressants, diagnostic criteria, and other factors. New studies may be needed to further investigate background risk of selected outcomes and risk factors in solid organ transplant patients.

BACKGROUND

- Improved surgical techniques
- Immuno-suppressive agents
- Longer survival after allograft transplantation
- To provide context for clinical trials
 - Needed data on background rates of various post-transplant outcomes
- Literature review goal: to assess current evidence about risks from observational studies

OBJECTIVE

- The objective of this study was to systematically review the risk of selected outcomes after adult solid organ transplantation

METHODS

- Used Medline, Cochrane database, Embase (Medline most useful)
- Target studies:
 - Epidemiologic, observational (not trials)
 - Published 1998 - April, 2005
 - Transplanted solid organs (lung, heart, liver, pancreas, kidney)
 - Adult organ recipients (age ≥ 18 years)
 - From US, Western Europe, Japan
- Outcomes of interest
 - Neoplasms
 - Serious infections (e.g., requiring hospitalization)
 - Graft, patient survival
 - New cardiovascular risks post-transplant:
 - Hypertension
 - Diabetes
 - Dyslipidemia
- Large amount of literature - required representation all above outcomes in a final set of 40 articles

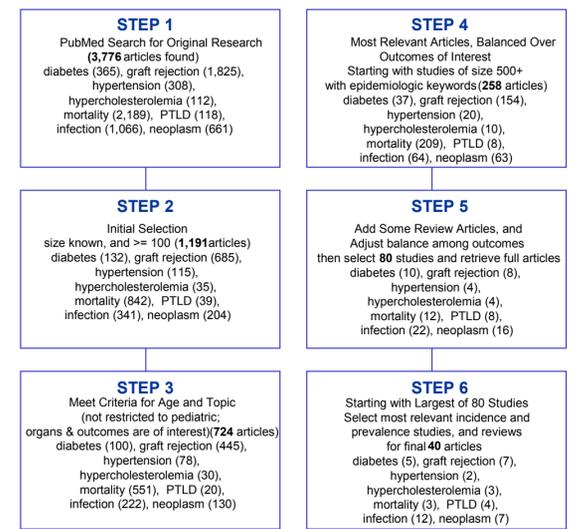
Search Strategy

- Medline MeSH terms
 - e.g., organ transplantation AND neoplasms
- Excluded abstracts if:
 - Not a targeted organ (e.g., bone marrow)
 - Not formal study (e.g., case reports)
 - Pediatric only (age < 18 years)
 - Not US, Western Europe, Japan
 - Not in English

Search Output

- 3,776 abstracts resulted from searches
- To process this large volume of reports, we first looked at studies with ≥ 100 subjects (1,191 studies, or 31.5%)
- Of the 1,191 studies, 724 (60.8%) were on adults, and on the organs and outcomes of interest

Figure 1. Process of Selection of 40 Studies



METHODS (Con'td)

Most Relevant Studies

- Focused on those most likely to be large, observational, epidemiologic studies
 - Had epidemiologic keywords (incidence, prevalence, statistics, etc.)
 - Study size ≥ 500
- 80 full articles obtained for detailed review
- Final set of 42 articles (including reviews) distributed over all target outcomes

Table 1: Characteristics of 40 Selected Study Reports

Main Outcome Type	N of Studies by Publication Type		N, % of Total
	Original	Review	
Diabetes	3	2	5 12.5
Dyslipidemia	2	0	2 5
Graft rejection/failure	6	0	6 15
Hypertension	2	0	2 5
Infection	10	2	12 30
Neoplasm	5	2	7 17.5
PTLD	3	1	4 10
Mortality/survival	2	0	2 5
Total	33	7	40 100

Organ Type	N, % of Studies
All solid organs	4 10.0
Multiple	5 12.5
Kidney	27 67.5
Kidney-Pancreas	3 7.5
Heart	1 2.5
Total	40 100.0

Number of Patients	N, % of Studies
100-499	5 12.5
500-999	4 10.0
1,000-1,999	11 27.5
2,000-9,999	5 12.5
10,000 - 93,934	9 22.5
Reviews	6 15.0
Total	40 100.0

Country	N, % of Studies
United States	22 55.0
Canada	2 5.0
United Kingdom	2 5.0
Sweden	1 2.5
France	2 5.0
Spain	4 10.0
Reviews	7 17.5
Total	40 100.0

Last Year of Data Accrual	N, % of Studies
2003	1 2.5
2002	4 10
2001	2 5
2000	5 12.5
1999	5 12.5
1998	3 7.5
1997	9 22.5
1996	3 7.5
1990	1 2.5
Reviews	7 17.5
Total	40 100.0

Number of Observational Studies by Outcome

- Neoplasms (11)
 - 4 on PTLD, 7 on other neoplasms
- Serious infections (12)
- Graft or patient survival (9)
- Cardiovascular risks post-transplant (10)
 - Hypertension (2)
 - Diabetes (5)
 - Dyslipidemia (3)

Description of 42 Studies

- 67% about kidney transplants
- Number of subjects
 - 100-499: 12.5% of studies
 - 500-999: 10.0%
 - 1,000-1,999: 27.5%
 - ≥ 2,000 : 50.0%
- 55.0% of studies were from U.S.
- 82.5% of data collected < year 2000

RESULTS

Neoplasms

- Incidence of cancers other than non-melanoma skin cancer, per 100 renal recipients per year:
 - 0.93 (Agharhakar et al., 2004)
 - 0.89 (Danpanich et al., 1999)
- Cumulative incidence of cancers in renal recipients over 12-13 year follow-up:
 - 11.8% (Snanoudj et al., 2004)
 - 12.2% (Tremblay et al., 2002)

PTLD

- One study reported incidence rate of PTLD cases per 100,000 solid organ recipients as 43.5 (Domingo-Domenech et al., 2001)
 - in heart recipients, 357.1 cases
 - in liver recipients, 60.9 cases
 - in kidney recipients, 32.5
- Cumulative incidence estimates were reported (but length of follow-up not always specified):
 - 1% after heart transplant (Peraira et al., 2003)
 - 0.91% after solid organ transplant (Domingo-Domenech et al., 2001)
 - 2% after kidney transplant (Bates et al., 2003)
 - Cumulative incidence, one year, in USRDS & claims data, after kidney transplant: 0.53% for non-Hodgkin's lymphoma (Kasiske et al., 2004a)

Serious Infections

- Hospitalization rates per 100 kidney recipients per year during 3 years after transplant, from US Renal Data System linked to Medicare Claims:
 - Cytomegalovirus:
 - 1.26 admissions per 100 (Abbott et al., 2002a)
 - Bacterial septicemia:
 - 3.5 admissions per 100 (Abbott et al., 2001a)
 - Bacterial endocarditis:
 - 0.2 admissions per 100 (Abbott et al., 2001c)
 - Bacterial pneumonia:
 - 2.9 admissions per 100 (Tveit et al., 2002)
 - Fungal infection:
 - 0.52 admissions per 100 (Abbott et al., 2001b)

RESULTS

Graft Survival

- In kidney or kidney-pancreas transplants, allograft failure at one year:
 - 15% to 31% (Fong et al., 2003)
 - 6.1% (living donor), 12.3% (cadaveric donor) (Humar et al., 1999)
 - 7% to 13% (Mohan et al., 2003)
 - 16% (Snanoudj et al., 2004)

Patient Survival

- In kidney or kidney-pancreas transplants, mortality
 - at one year: 4% to 7% (Mohan et al., 2003)
 - at 3 years (Kasiske et al., 2000b):
 - 9% if < 25 pack-years of smoking
 - 18% if ≥ 25 pack-years of smoking
 - at five years: 13% (Snanoudj et al., 2004)

Hypertension

- Prevalent hypertension after kidney transplant
 - 33% (Snanoudj et al., 2004)
 - 42% (Kasiske et al., 2004b)
 - 82% (Campistol et al., 2004)

New Diabetes

- Risk at one year after kidney transplant
 - 13.4% kidney or liver (Heisel et al., 2004)
 - 7.1% (Cosio et al., 2001)
 - 16.0% USRDS & claims (Kasiske et al., 2003)
- Risk at 1.5 years after kidney transplant
 - 4.9% needed insulin and 6.2% needed oral antidiabetic agents at 1.5 years (First 2 et al., 2002)

Dyslipidemia

- At 6 to 12 months after kidney transplant:
 - Serum cholesterol > 240 mg/dL in 46% to 63% of patients (Chueh and Mahan, 2003)
- In 1st year after kidney transplant:
 - Serum cholesterol > 240 mg/dL in 58.4% of men and 64.1% of women (Kasiske et al., 2000a)

CONCLUSIONS

Reported rates and risks vary among studies due to:

- Type of patient populations
- Prevalence of viral infections
- Immunosuppressant exposures
- Diagnostic criteria for outcomes
- Amount of observed follow-up time

Other aspects of the transplant outcome literature:

- Many small clinical reports, few general population-based reports
- The literature is voluminous but relatively lacking in precise, valid epidemiologic measurements
- Many studies based in convenient populations (cases accumulated at transplant centers)
- Few reports give details of observed person-time
- Many reports give risk or cumulative incidence without specifying the time period to which these estimates apply
- Lack of common definitions or measurements limits comparison among studies from different locations
- Some very large studies based on national statistical reporting systems (USRDS)

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