ALEH Clinical Research Workshop: Cohort Studies

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Goal of talk: Understand a cohort vs a case-control study

Outcomes of living versus deceased donor liver transplantation in patients with chronic liver disease and hepatorenal syndrome (HRS) was compared using a matched pair study design. Thirty patients with HRS receiving a live donor liver transplantation (LDLT) and 90 HRS patients receiving a full graft deceased donor liver transplantation (DDLT) were compared. LDLT versus DDLT of patients with HRS was associated with decreased peak aspartate aminotransferase levels (339 ± 214 vs. 935 ± 1253 U/L; p = 0.0001), and similar 7-day bilirubin (8.42 ± 7.89 vs. 6.95 ± 7.13 mg/dL; p = 0.35), and international normalized ratio levels (1.93 ± 0.62 vs. 1.78 ± 0.78; p = 0.314). LDLT vs. DDLT had a decreased intensive care unit (2 [1–39] vs. 4 [0–93] days; p = 0.004), and hospital stay (17 [4–313] vs. 26 [0–126] days; p = 0.016) and a similar incidence of overall postoperative complications (20% vs. 27%; p = 0.62). No difference was detected between LDLT and DDLT patients regarding graft survival at 1 (80% vs. 82%), at 3 (69% vs. 76%) and 5 years (65% vs. 76%) (p = 0.63), as well as patient survival at 1 (83% vs. 82%), 3 (72% vs. 77%) and 5 years (72% vs. 77%) (p = 0.93). The incidence of chronic kidney disease post-LT (10% vs. 6%; p = 0.4) was similar between both groups. LDLT results in identical long-term outcome when compared with DDLT in patients with HRS.

Results of Liver Transplantation With Donors Older Than 70 Years: A Case-Control Study

J.M. Álamo, L. Barrera, L.-M. Marín, C. Bernal, G. Suárez, J. Serrano, M.A. Gómez, and F.J. Padillo

ABSTRACT
Older donors are a growing part of the total pool but no definite consensus exists on the age limit for their acceptance. This retrospective case-control uncenter study compared the outcomes of 72 orthotopic liver transplantations (OLTs) from April 1990 to April 2010 using donors older than 70 years versus 738 chronologically correlated OLTs performed with donors younger than 60 years. The percentage of refusal was greater among older than younger donors (48.2 vs 14.3%; P < .001). No difference was observed in mean cold ischemia times between older (370.5 minutes) versus younger groups (389.2 minutes), or in postoperative complications of rejection or renal insufficiency except for sepsis and mortality. Long-term survival was lower among transplant recipients from donors older than 70 years (P = .001) and these cases showed more blood requirements associated with prolonged cold ischemia (P = .02). Multivariate analysis revealed graft dysfunction, mortality, and reduced survival to be associated with donor weight and recipient MELD (Model for End-stage Liver Disease) (P < .05). Interestingly, the mortality related to hepatitis C virus recurrence was not greater among patients whose donors were older than 70. Septuagenarians’ livers can be used safely, but careful donor and recipient evaluation are required to avoid additional risk factors.
Types of observational study designs

- **Descriptive studies**
  - **Correlational**
    - Compare disease frequencies between different groups during a given time period or over time
    - Look at data from 2016
    - Compare deaths from liver disease in each country in South America and success in the Copa America
    - Hypothetical conclusion: Higher rates of deaths from liver disease in Argentina were correlated with losing to Chile in the Copa America
    - Ecological fallacy: Higher death rates may be due to higher burden of hepatitis C
  - **Cross-sectional**
    - Individual exposure and outcome collected at same time
    - Collect data from individuals at same time
    - Cannot determine if exposure is related to outcome
Observational analytic study designs

• Cohort study
  – Individuals with an exposure to a suspected agent (i.e., therapy, surgery, disease) are compared to similar individuals without, looking for outcomes
    • Exposed versus unexposed

• Case-control study
  – Individuals with an outcome (cases) compared to similar individuals without (controls), looking for exposures
    • Diseased versus non-diseased
Cohort studies: Prospective or Retrospective?

- **Prospective**
  - Outcome occurs after investigation is initiated
  - Enroll all OLT recipients at time of transplant
    - Exposure is pre-transplant diabetes
    - Follow-up for outcome of MI

- **Retrospective**
  - Outcome occurs before investigation is initiated
  - Compare risk of MI in diabetics vs non-diabetics transplanted between 2005-2010
Why cohort studies preferable to case-control

• Can evaluate rare exposures
  – Toxin exposure in workers at a specific factory
• Design phase
  – Don’t need to match cases and controls
• Can estimate incidence rather than odds
A comparison of the approaches

Prospective Cohort Study

Exposure
Yes
No

Investigator
At start

Outcome
?
?

Retrospective Cohort Study

Exposure
Yes
No

Outcome
?
?

Investigator
At start

Case-control Study

Exposure
?
?
?

Outcome
Yes (cases)
No (controls)

Investigator
At start
Cohort studies

- **Purpose**
  - To test hypotheses regarding outcome causation
    - Patients with NASH have a higher risk of post-transplant cardiac events
    - Cannot prove cause and effect; **only associations**

- **Cohort**
  - Individuals defined by exposure prior to appearance of the disease under study
    - Disease (NASH vs non-NASH)
    - Treatment (terlipressin vs MAO)
  - Observed over time to determine and compare the occurrence and frequency of disease among them
Cohort design overview

Cross-sectional study or screening to exclude those with the condition

Reference population free of condition

Sample

With the characteristic

Developed the condition

Did not develop condition

Without the characteristic

Developed the condition

Did not develop condition
Prospective cohort studies

- Cohort is selected from active pool of participants
  - Factory workers
  - Transplant recipients from time of transplant
- Cohort is followed over time to some endpoint
  - Development of outcome
  - Loss to follow-up
  - Death
- Members of cohort are compared with each other for outcome frequency
- Transplant recipients with NASH (exposed) vs alcohol (unexposed)
Characteristics of prospective cohort studies

• Strengths
  – Can establish that exposure occurred prior to outcome (temporality important in establishing causation)
  – Investigator can make accurate measurements

• Weaknesses
  – Expensive and inefficient in rare outcomes
  – Causal inference challenging
Retrospective cohort studies

• Cohort constructed from existing records
• Measurements, follow-up, and outcomes occurred in past
• Identify subjects based on exposure of interest
• UNOS database of all transplant recipients between 2010-2012
  – Compare NASH vs non-NASH for death
Characteristics of retrospective cohort studies

• Strengths
  – Shared with prospective cohort studies, but less time-consuming
  – May be more efficient than prospective
  – Can use existing data
    • Efficiency
    • Cost

• Weaknesses
  – Lack of control in sampling, availability of data, and potentially incomplete follow-up
    • Missing data
    • Inappropriate data measures
Statistical approaches to cohort studies

• Risk
  – \( \frac{\text{N who develop outcome}}{\text{N at risk}} \)

• Odds
  – \( \frac{\text{N who develop outcome}}{\text{N who do not develop outcome}} \)

• Rate
  – \( \frac{\text{N who develop outcome}}{\text{Person-time at risk}} \)

• Prospective cohort study of 1,000 people followed for 2 years for development gastric cancer→16 new cases
  – Risk: \( \frac{16}{1,000}=0.016 \)
  – Odds: \( \frac{16}{984}=0.0163 \)
    • Odds \( \approx \) risk for rare outcome
  – Rate: \( \frac{16}{1,992}=0.008 \) cases/person-year
Example of retrospective cohort study and potential limitations


- Retrospective cohort study of all US adult OLT recipients between 2002-2012
- Source of data
  - OPTN/UNOS data
- Cohort: All adult transplant recipients
- Exposed: Living donor transplant recipients
- Unexposed: Deceased donor transplant recipients
- Outcomes: Death and graft failure
- Conclusions: LDLT recipients have lower risk of death or graft failure
Limitations of this type of retrospective cohort study

- Use multivariable models to account for confounders
  - I.e., are LDLT recipients "less sick"
  - Adjust for MELD score, age, functional status, ...
- Confounding by indication
  - Patients who get LDLT may be inherently different
  - Constrained by collected data for adjustments
  - Unmeasured confounders
- UNOS vs A2ALL data
- Information bias
  - UNOS data collected for center reporting
  - Clinical variables not well captured
- Frailty vs Karnofsky score
  - Lower MELD
  - Lower risk of post-transplant death
  - LDLT recipients
  - Lower risk of post-transplant death
Causal inferences in observational studies

- True association
- Spurious associations
  - Chance: Random error
- Real associations but not causal
  - Effect-cause
    - Needs biologic plausibility
    - Heavy exercise associated with MI $\rightarrow$ people who have had MIs exercise more
  - Confounding
    - Third factor is real cause of outcome $\rightarrow$ predictor associated with third cause
    - Coffee drinking and pancreatic cancer (cigarette smoking is confounder)
Dealing with confounders: Analytic phase

- **Stratification** (compare exposed vs unexposed by gender)
- **Assess for effect modification** (interaction)
- **Adjustment**
  - Multivariable techniques
  - Use all information simultaneously
  - Complexity in analysis and interpretation
- **Propensity scores**
  - Account for confounding by indication (i.e., patients who are less frail are more likely to get LDLT)
    Predicts receipt of treatment
  - Match patients based on probability of getting treatment (quasi-experimental)
Statistical modeling in cohort studies

- Why do modeling
  - Adjust for confounders
  - Evaluate for interaction
  
- Shouldn’t be necessary in correctly performed RCT
  - Should have balance of known and unknown confounders

- Binary outcome
  - Don’t care about time
  - 30-day mortality for alcoholic hepatitis
  - 1-year risk of ESRD post-transplant
  - Logistic regression

- Time to event
  - Time matters
  - Post-transplant survival
    - Death at 30 days and death at 4 years different
Logistic vs Cox regression

• Retrospective cohort study of 200 OLT recipients
  – Exposure: HCV vs EtOH
  – Outcome: 5-year post-transplant survival

• Overall outcomes
  – 100 with HCV: 50 died at 5 years, 50 alive at 5 years
  – 100 with EtOH: 50 died at 1 month, 50 alive at 5 years

• Impact of outcomes
  – Binary: 50/100 (50%) patients die in each group
  – Logistic regression: OR for HCV: 1.00 (0.57-1.74)
  – Time-to-event: HR for HCV: 0.66 (0.45-0.98)
Living vs. Deceased Donor Liver Transplantation Provides Comparable Recovery of Renal Function in Patients With Hepatorenal Syndrome: A Matched Case–Control Study

Outcomes of living versus deceased donor liver transplantation in patients with chronic liver disease and hepatorenal syndrome (HRS) was compared using a matched pair study design. Thirty patients with HRS receiving a live donor liver transplantation (LDLT) and 90 HRS patients receiving a full graft deceased donor liver transplantation (DDLT) were compared. LDLT versus DDLT of patients with HRS was associated with decreased peak aspartate aminotransferase levels (339 ± 214 vs. 935 ± 1253 U/L; p = 0.0001), and similar 7-day bilirubin (8.42 ± 7.89 vs. 6.95 ± 7.13 mg/dL; p = 0.35), and international normalized ratio levels (1.93 ± 0.62 vs. 1.78 ± 0.78; p = 0.314). LDLT vs. DDLT had a decreased intensive care unit (2 [1–39] vs. 4 [0–93] days; p = 0.004), and hospital stay (17 [4–313] vs. 26 [0–126] days; p = 0.016) and a similar incidence of overall postoperative complications (20% vs. 27%; p = 0.62). No difference was detected between LDLT and DDLT patients regarding graft survival at 1 (80% vs. 82%), at 3 (69% vs. 76%) and 5 years (65% vs. 76%) (p = 0.63), as well as patient survival at 1 (83% vs. 82%), 3 (72% vs. 77%) and 5 years (72% vs. 77%) (p = 0.93). The incidence of chronic kidney disease post-LT (10% vs. 6%; p = 0.4) was similar between both groups. LDLT results in identical long-term outcome when compared with DDLT in patients with HRS.

• Is the description of this study correct?
• What type of study is this?
• Do you agree with their conclusions?
What is the study design?

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Conclusion

• Cohort studies very powerful tool
• Comparisons are made based on exposure, evaluating for outcome
• Can be prospective or retrospective
• Important to always spell out what you are trying to evaluate
  – If exposure is associated with a specific outcome, OR
  – If outcome is associated with a specific exposure