Coexistence of Alcoholic Liver Disease and Alcoholic Pancreatitis

AJAY SINGHVI
MENTOR: DHIRAJ YADAV
CAPER PANCREAS SCHOLAR PRESENTATION
Alcohol use is a common problem worldwide

Alcohol use disorder affects approximately 6.2% or 15.1 million adults in the United States

Long standing alcohol use is a known cause of liver and pancreatic damage, leading to cirrhosis or chronic pancreatitis respectively.

Research has yielded variable results regarding the prevalence of the coexistent alcohol-related pancreatic and liver conditions

National Institute on Alcohol Abuse and Alcoholism, U.S. Department of Health and Human Services
In clinical practice, the coincidence of both liver cirrhosis and chronic pancreatitis is uncommon. These diseases share few risk factors other than alcohol consumption. No significant overlap in risk factors in Japanese alcoholics. Duration of alcohol use required for disease development is greater in liver cirrhosis than in chronic pancreatitis.
However, asymptomatic alcoholic liver disease may be frequent in chronic alcoholic pancreatitis (and vice versa).

- If hepatic pathology unrecognized, surgical procedures can lead to complications that aggravate the clinical course.

- Development of ascites and varices as a sequela of portal hypertension increases morbidity and mortality in patients with both disease processes.

Controversy exists regarding the frequency of coincident chronic pancreatitis and liver cirrhosis in alcoholic patients.

Conflicting findings may be due to differences in:

- Variable definitions of alcohol related conditions studied
- Methodology: retrospective vs prospective studies
- Evaluation of diagnostic parameters (i.e. clinical, functional, radiographic, or histopathological criteria)
Aims: Systematic Review

- Determine robust prevalence estimates of coexistent
  - alcoholic cirrhosis and chronic pancreatitis
  - alcoholic liver disease and alcoholic pancreatitis among patients with a diagnosis of alcoholism
- Identify alcohol-related diseases that associate with alcoholic liver disease and alcoholic pancreatitis
Inclusion and Exclusion criteria

Inclusion criteria
- Studies that allowed for the calculation of prevalence of coexistent disease for alcoholic pancreatitis in alcoholic liver disease or alcoholic liver disease in alcoholic pancreatitis
- Human studies

Exclusion criteria
- Non-English studies
- Review articles and case studies/series < 25 patients
- Abstracts without a full manuscript
- Duplicate publications
2000 articles identified through database searches (using MEDLINE, Embase and Web of Science) between 1965-2018.

**1968 articles excluded:**
- Duplicate studies between databases (n=379)
- Case reports OR series less than 25 patients (n=257)
- Review articles (n=181)
- Abstract or lecture (n=179)
- Non-English studies (n=236)
- Animal models/In Vitro studies (n=42)
- Did not meet inclusion criteria (n=694)

32 articles selected for full text review

**3 articles excluded:**
- Prevalence reported as subgroup analysis of mortality (n=1)
- Prevalence reported based on discharge diagnoses (n=1)
- Full text not available (n=1)

29 articles selected for final review

- Non-autopsy studies (n=24)
- Autopsy studies (n=5)
Results

- Majority of studies were from Europe (59%) or North America (21%)
- Roughly 50% were published after year 2000
- Most included no or few female subjects
- Number of subjects
  - Alcoholic cirrhosis (n=2211 from 15 studies)
  - Chronic pancreatitis (n=652 from 11 studies)
Prevalence of Alcoholic Chronic Pancreatitis in Alcoholic Cirrhosis

Random effects model
Heterogeneity: $I^2 = 92\%$, $\tau^2 = 0.8194$, $p < 0.01$

<table>
<thead>
<tr>
<th>Study</th>
<th>Events per 100 observations</th>
<th>Chronic Pancreatitis</th>
<th>Cirrhosis</th>
<th>Prevalence (%)</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adams 1980</td>
<td>62</td>
<td>105</td>
<td>59.0</td>
<td>[49.0; 68.5]</td>
<td>9.3%</td>
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</tr>
<tr>
<td>Agrawal 2014</td>
<td>32</td>
<td>292</td>
<td>11.0</td>
<td>[7.6; 15.1]</td>
<td>10.4%</td>
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<tr>
<td>Aparisi 2008</td>
<td>1</td>
<td>57</td>
<td>1.8</td>
<td>[0.0; 9.4]</td>
<td>0.4%</td>
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<tr>
<td>Hastier 1999</td>
<td>14</td>
<td>72</td>
<td>19.4</td>
<td>[11.1; 30.5]</td>
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<td>Kochhar 2003</td>
<td>12</td>
<td>31</td>
<td>38.7</td>
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<td>2.7%</td>
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<tr>
<td>Pace 2009</td>
<td>33</td>
<td>183</td>
<td>18.0</td>
<td>[12.8; 24.4]</td>
<td>9.9%</td>
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<tr>
<td>Renner 1984</td>
<td>2</td>
<td>80</td>
<td>2.5</td>
<td>[0.3; 8.7]</td>
<td>0.7%</td>
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<tr>
<td>Spicak 2012</td>
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<td>35</td>
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<td>147</td>
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<td>Darstein 2014</td>
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<td>20</td>
<td>35.0</td>
<td>[15.4; 59.2]</td>
<td>1.7%</td>
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<tr>
<td>Davis 1969</td>
<td>1</td>
<td>26</td>
<td>3.8</td>
<td>[0.1; 19.6]</td>
<td>0.4%</td>
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<tr>
<td>Hayakawa 1991</td>
<td>2</td>
<td>148</td>
<td>1.4</td>
<td>[0.2; 4.8]</td>
<td>0.7%</td>
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<tr>
<td>Martin 1989</td>
<td>7</td>
<td>10</td>
<td>70.0</td>
<td>[34.8; 93.3]</td>
<td>0.8%</td>
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<tr>
<td>Testoni 1984</td>
<td>22</td>
<td>222</td>
<td>9.9</td>
<td>[6.3; 14.6]</td>
<td>7.2%</td>
<td></td>
</tr>
<tr>
<td>Wehmeyer 2017</td>
<td>2211</td>
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<td>[10.4; 24.5]</td>
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Prevalence of Alcoholic Chronic Pancreatitis in Alcoholic Cirrhosis (autopsy studies removed)

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<td>Wehmeyer 2017</td>
<td></td>
<td>22</td>
<td>222</td>
<td>9.9</td>
<td>[6.3; 14.6]</td>
<td>30.9%</td>
</tr>
</tbody>
</table>

**Random effects model**

Heterogeneity: $I^2 = 87\%$, $\tau^2 = 1.1082$, $p < 0.01$

**Total**

|           | 700 | 15.5 | [8.0; 27.7] | -- |

Prevalence (%)

- Chronic Pancreatitis: 1.8 [0.0; 9.4]
- Cirrhosis: 19.4 [11.1; 30.5]
- Prevalence in Alcoholic Cirrhosis: 15.5 [8.0; 27.7]
Prevalence of Alcoholic Cirrhosis in Alcoholic Chronic Pancreatitis

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<tr>
<th>Study</th>
<th>Events per 100 observations</th>
<th>Cirrhosis</th>
<th>Chronic Pancreatitis</th>
<th>Prevalence (%)</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adams 1980</td>
<td>62</td>
<td>83</td>
<td>74.7 [64.0; 83.6]</td>
<td>16.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aparisi 2008</td>
<td>3</td>
<td>53</td>
<td>5.7 [1.2; 15.7]</td>
<td>2.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chebli 1997</td>
<td>9</td>
<td>32</td>
<td>28.1 [13.7; 46.7]</td>
<td>6.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutta 1978</td>
<td>15</td>
<td>46</td>
<td>32.6 [19.5; 48.0]</td>
<td>10.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pace 2009</td>
<td>33</td>
<td>85</td>
<td>38.8 [28.4; 50.0]</td>
<td>20.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spicak 2012</td>
<td>11</td>
<td>66</td>
<td>16.7 [8.6; 27.9]</td>
<td>9.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frossard 2013</td>
<td>8</td>
<td>28</td>
<td>28.6 [13.2; 48.7]</td>
<td>5.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gullo 1995</td>
<td>7</td>
<td>50</td>
<td>14.0 [5.8; 26.7]</td>
<td>6.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jalleh 1991</td>
<td>0</td>
<td>40</td>
<td>0.0 [0.0; 8.8]</td>
<td>0.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesur 1993</td>
<td>5</td>
<td>48</td>
<td>10.4 [3.5; 22.7]</td>
<td>4.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montalto 1992</td>
<td>18</td>
<td>121</td>
<td>14.9 [9.1; 22.5]</td>
<td>15.9%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Random effects model
Heterogeneity: $I^2 = 91\%$, $\tau^2 = 1.1898$, $p < 0.01$

Adams 1980
Aparisi 2008
Chebli 1997
Dutta 1978
Pace 2009
Spicak 2012
Frossard 2013
Gullo 1995
Jalleh 1991
Lesur 1993
Montalto 1992

652 21.5 [12.0; 35.6] --
Prevalence of Alcoholic Cirrhosis in Alcoholic Chronic Pancreatitis (autopsy studies removed)

**Study** | Events per 100 observations | Cirrhosis | Chronic Pancreatitis | Prevalence (%) | 95% CI | Weight |
---|---|---|---|---|---|---|
Aparisi 2008 | 3 | 53 | 5.7 | [1.2; 15.7] | 4.7% |
Chebli 1997 | 9 | 32 | 28.1 | [13.7; 46.7] | 10.7% |
Dutta 1978 | 15 | 46 | 32.6 | [19.5; 48.0] | 16.7% |
Spicak 2012 | 11 | 66 | 16.7 | [8.6; 27.9] | 15.1% |
Frossard 2013 | 8 | 28 | 28.6 | [13.2; 48.7] | 9.4% |
Gullo 1995 | 7 | 50 | 14.0 | [5.8; 26.7] | 9.9% |
Jalleh 1991 | 0 | 40 | 0.0 | [0.0; 8.8] | 0.8% |
Lesur 1993 | 5 | 48 | 10.4 | [3.5; 22.7] | 7.4% |
Montalto 1992 | 18 | 121 | 14.9 | [9.1; 22.5] | 25.3% |

**Random effects model**

Heterogeneity: $I^2 = 65\%$, $t^2 = 0.2841$, $p < 0.01$

484 | 16.9 | [11.5; 24.3] | --
Summary of Results

- Pooled prevalence of Chronic Pancreatitis in overall Alcoholic Cirrhosis was 16.2% (95% CI 10.4-24.5)
  - After excluding autopsy studies was 15.5% (95% CI 15.5-27.7)

- Pooled prevalence of Alcoholic Cirrhosis in Chronic Pancreatitis overall was 21.5% (95% CI 12-35.6)
  - After excluding autopsy studies was 16.9% (95% CI 11.5-24.3)
Limitations of this systematic review

- Small sample sizes of individual studies
- Many of the studies were retrospective
- Geographical variation across countries and continents
- Comparing studies from different decades
- Variable criteria for defining alcoholic pancreatitis and alcoholic cirrhosis
  - Parameters used included clinical, functional, imaging, or histopathological criteria
- Few women
Administrative Data Study

- Study the prevalence of coexistent alcoholic pancreatitis and alcoholic cirrhosis
  - Larger sample sizes
  - Homogenous population
  - More female patients
Primary Aim: To determine the prevalence of alcohol-related comorbidities in patients with a diagnosis of alcoholism.

- Alcoholic pancreatitis (acute/chronic)
- Alcoholic hepatitis, Alcoholic cirrhosis
- Coexistence of alcoholic cirrhosis + alcoholic pancreatitis

Secondary Aim: To determine the prevalence of additional alcohol-related conditions (cardiomyopathy, withdrawal/DTs, Wernicke/Korsakoff, neuropathy) among patients with alcoholism
Study Design

- Retrospective cohort study
- Source population:
  - University of Pittsburgh Medical Center (UPMC) Medical Archival Retrieval System (MARS) to identify the patient cohort (2006-2015).
  - MARS collects all data from UPMC (outpatient, inpatient, billing)
  - MARS will be used to screen all UPMC data using ICD-9/10 diagnosis codes
1. **Group A: Alcoholism**
   - Neuropsychiatric manifestations of Alcohol
   - Toxic Effects of Alcohol not otherwise specified
   - Sexual manifestations of alcohol
   - Cardiac manifestations of alcohol
   - Alcohol use disorder
2. Group B: Pancreatitis
   - Acute pancreatitis (unspecified etiology)
   - Acute pancreatitis, etiology biliary
   - Acute pancreatitis, etiology alcohol
   - Acute pancreatitis, etiology drug induced
   - Chronic pancreatitis, etiology alcohol
   - Chronic pancreatitis, (unspecified etiology)
3. Group C: Alcoholic Liver Disease
   - Alcoholic hepatitis
   - Alcoholic cirrhosis
   - Alcoholic liver disease (unspecified)
   - Alcoholic fatty liver
   - Alcoholic liver failure
Group D: Other Liver Diseases
- Hepatitis B (acute and chronic)
- Hepatitis C (acute and chronic)
- Hepatitis D
- Unspecified viral hepatitis (acute and chronic)
- Fatty liver disease
- Hepatitis (not otherwise specified)
- Cirrhosis not otherwise specified
- Autoimmune hepatitis
- Biliary cirrhosis
- Liver failure, etiology not specified
Variables of interest

- Age at initial diagnosis
- Gender
- Race
- Inpatient admission (Y/N) for any of these diagnoses
  - Inpatient code that prompted admission
  - Number of inpatient admissions for each diagnosis
- Duration of contact with UPMC system
- Decompensated liver disease
Analysis Plan

- Calculate prevalence of individual condition and overlap
- Stratify prevalence results based on age, gender, and race
- Compare demographic and other relevant variables between groups
- Sensitivity analyses
  - Duration of follow-up in UPMC system, hospital type
Strengths and Limitations

Strengths:
- Large data set
- Ability to provide data on women

Limitations:
- Use of ICD-9/10 diagnosis codes
- Unable to capture data for some outpatient physician practices
- Some hospitals came into UPMC system later during study period
Where are we now?

- We now have the data set
- Working on developing a detailed analysis plan