# Epidemiology of Fibrolamellar Hepatocellular Carcinoma: A Targeted Literature Review

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## BACKGROUND

- **FLC is an ultra-rare primary liver cancer** (~0.02 per 100,000).
- **Affects adolescents and young adults** (mean/median age 25–27 years in most studies) without chronic liver disease or cirrhosis.
- **AFP is elevated in only 15.8–37.2%** of patients, unlike traditional HCC.
- Robust epidemiologic evidence is essential for burden assessment, HTA and health economic modeling.

**OBJECTIVE**
Synthesize published epidemiologic evidence on FLC to establish baseline metrics for HTA and economic evaluations.

## METHODS

Targeted literature review of PubMed and Google Scholar; English-language studies published after 2000.

**1,173 records identified**
PubMed & Google Scholar

↓

**1,123 excluded**
at title / abstract screening

↓

**50 full-text reports assessed**
43 excluded (1 wrong population, 42 no outcome); 1 not retrieved

↓

**7 key studies included**
6 full-text articles + 1 conference abstract

## ELIGIBILITY CRITERIA

| Domain | Inclusion criteria |
|---|---|
| **Population** | Patients with histologically / pathologically confirmed FLC / FL-HCC |
| **Intervention** | N/A (descriptive epidemiological review) |
| **Study design** | Population registries, EMR databases, cohorts (≥10 patients) |
| **Outcomes** | Incidence, prevalence, demographics, stage, survival, mortality risk |
| **Limits** | English language; published after year 2000 |

## RESULTS: INCLUDED STUDIES (7 STUDIES)

| Study | Cases | Incidence / 100,000 | Key demographics / features |
|---|---|---|---|
| **Ramai 2021** SEER 00-16 | **300** | 0.020 overall (M: 0.025, F: 0.016) | Median age 27; 61.3% male; 78.0% White; bimodal peaks (15–19 & 70–74 yrs) |
| **Eggert 2013** SEER 00-10 | **191** | 0.020–0.025 (APC +1.3%) | Cross-ethnic consistency (non-Hispanic White 0.022, Black 0.025, API 0.022) |
| **El-Serag 2004** SEER 1973+ | **68** | 0.020 (95% CI 0.01–0.02) | Mean age 39; 63.2% ≤40 yrs; 48.5% male; 85.3% non-Hispanic White |
| **Zack 2023** EMR 12-21 | **33** | 0.185 US national (0.017 regional) | Mean age 25.5; 100% <50 yrs; est. 602 ± 110 national US cases / yr |
| **Alnabulsi 2024** SEER 00-20 | **362** | FLC incidence: 1.9% (2005) → 5.8% (2020) | Median age 27; 62.2% male; 78.2% White; 26.4% Stage IV; 15.8% AFP+ |
| **Qiu 2023** SEER 00-15 | **213** | Not reported | Mean age 33; 61.0% male; 78.9% White; 44.6% Stage IV; 37.2% AFP+ (of known) |
| **Yamashita 2016** Single centre 90-15 | **65** | Not reported | Median age 25; 48% male; 86% Caucasian; resected: 46% Stage IV, 43% nodal mets |

## CRITICAL EVIDENCE GAP

# ZERO

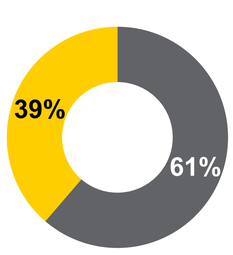
**population-based prevalence estimates; none reported by any of the 7 studies**

No prevalence data across all database searches creates substantial uncertainty for budget impact models, economic evaluations and HTA submissions for emerging FLC therapies.

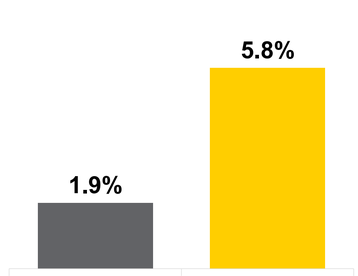
**Note:** 5 of 7 studies use SEER data (4 with overlapping years from 2000), so case counts are not additive.

## INCIDENCE & DEMOGRAPHICS

**Sex (%) – Ramai 2021**



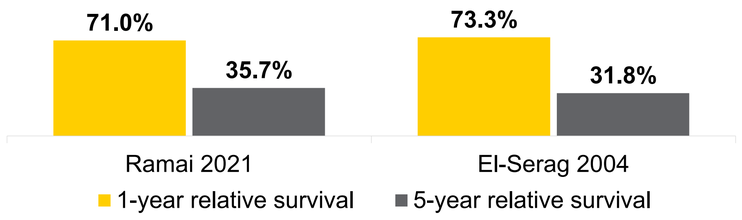

**FLC incidence (%)**




- **Male preponderance:** 61.0–62.2% (Ramai, Qiu, Alnabulsi) vs 48–48.5% (Yamashita, El-Serag).
- **Bimodal age peaks:** 15–19 yrs (primary), 70–74 yrs (secondary).
- **Racial pattern:** uniformly low incidence (non-Hispanic White 0.022, Black 0.025, API 0.022 per 100,000; Eggert 2013).

## SURVIVAL & TREATMENT

**Relative survival (%): 1-year vs 5-year**



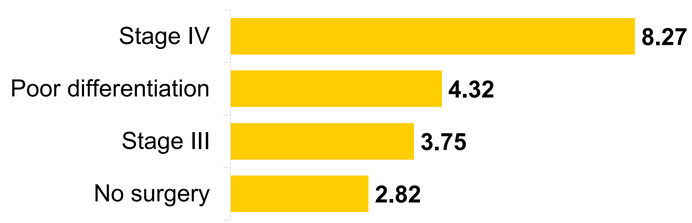

**24.5 mo**
Median overall survival (Alnabulsi 2024)

**92 vs 21 mo**
Median OS, Stage I vs Stage IV

**SURGICAL RESECTION ADVANTAGE**
5-yr relative survival **58.2%** with resection vs **7.4%** without surgery (Eggert 2013, all ages)
Resected FLC: 5-yr OS **58%**; 86% recurred; re-resection of recurrence: median OS **122 vs 37 mo** (Yamashita 2016)

## PROGNOSTIC FACTORS

**Hazard ratio for mortality (multivariate Cox regression; Ramai 2021)**




- **Curative therapy** (resection / transplant) cut 1-year mortality risk by 68% (El-Serag 2surgery004).
- **Treatment:** 50.3%, 48.1% chemotherapy, 25% multimodal; median 1.0 month to treatment (Alnabulsi 2024).
- **Vs HCC (PSM):** median OS 26 vs 11 mo (p=0.042); CSS 28 vs 14 mo (p=0.083) (Qiu 2023).
- **Resected FLC:** vascular invasion → 3-yr RFS 9% vs 35% (p=0.034); multiple tumours → 5-yr OS 25% vs 67% (p=0.001) (Yamashita 2016).

## CONCLUSIONS & HTA IMPLICATIONS

1. **Ultra-rare burden**
FLC (~0.02 per 100,000) needs specialized regulatory pathways, trial designs and flexible HTA decision rules.

2. **Rising incidence**
FLC incidence rose from 1.9% in 2005 to 5.8% in 2020 (Alnabulsi 2024).

3. **Diagnostic pearl**
Low AFP positivity (15.8–37.2%) calls for histological validation in young patients with liver masses.

4. **Urgent registry need**
Multinational registries are needed to quantify prevalence and economic burden and to support pricing & reimbursement.

## REFERENCES & FUNDING

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