

# Global economic burden of metabolic dysfunction-associated steatohepatitis with cirrhosis: a systematic literature review

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Aim

To perform a systematic literature review (SLR) to identify data on the economic burden of metabolic dysfunction-associated steatohepatitis (MASH) with cirrhosis.

## Introduction

- Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease and is estimated to affect more than one in three adults worldwide.<sup>1</sup>
- The progressive form of MASLD is MASH, in which liver fibrosis may be absent (fibrosis stage F0), or patients may have early fibrosis (F1), clinically significant fibrosis (F2/F3) or cirrhosis (F4).<sup>2</sup>
- The US Food and Drug Administration and the European Medicines Agency have approved treatments for MASH with stage F2 or F3 fibrosis, but there are no approved treatments for the most severe disease stage, cirrhosis (F4), which may be compensated or decompensated.<sup>3-5</sup>
- The lack of approved treatments and delays in diagnosis limit opportunities to prevent or reverse disease progression prior to the development of cirrhosis, or to prevent decompensation in cirrhosis.<sup>6</sup>

## Methods

- An SLR was conducted in line with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and registered with PROSPERO in 2024 (CRD42024586520). The SLR identified studies reporting on clinical outcomes, and the humanistic and economic burden of MASH with cirrhosis, which were published between 1 January 2014 and 25 July 2024.
- The titles and abstracts of the studies identified by searches in Embase, MEDLINE and the Cochrane Library were screened by a single reviewer to determine whether they met the predefined eligibility criteria summarized in **Table 1**.
- All studies that passed through title and abstract screening were obtained as full publications and reassessed against the eligibility criteria.
- Data were extracted from key papers determined to be relevant at full-text review.

Table 1: Eligibility criteria for the SLR

|                         |  |
|-------------------------|--|
| Populations             | Patients with MASH at stage F4 (cirrhosis including compensated and decompensated cirrhosis)   |
| Intervention/comparator | No restriction   |
| Outcomes                | Outcomes falling under the following categories (for full list of specific outcomes see PROSPERO record CRD42024586520) <ul style="list-style-type: none"><li>Clinical outcomes</li><li>Epidemiologic outcomes<sup>a</sup></li><li>Humanistic burden</li><li>Economic burden</li></ul> |
| Study design            | <ul style="list-style-type: none"><li>Clinical trials and observational studies</li><li>Animal studies and <i>in vitro</i> studies were excluded</li></ul>   |
| Date restrictions       | 1 January 2014–present <sup>b</sup>  |
| Language restrictions   | English language only  |
| Publication type        | <ul style="list-style-type: none"><li>All primary publications, SLRs and meta-analyses</li><li>Case studies, case reports and review articles were excluded</li></ul>  |
| Country                 | No restriction   |

<sup>a</sup>Electronic searches did not include specific terms for all epidemiologic outcomes, but any relevant studies or data on these outcomes were included. <sup>b</sup>Searches were carried out on 25 July 2024. F4, fibrosis stage 4; MASH, metabolic dysfunction-associated steatohepatitis; SLR, systematic literature review.

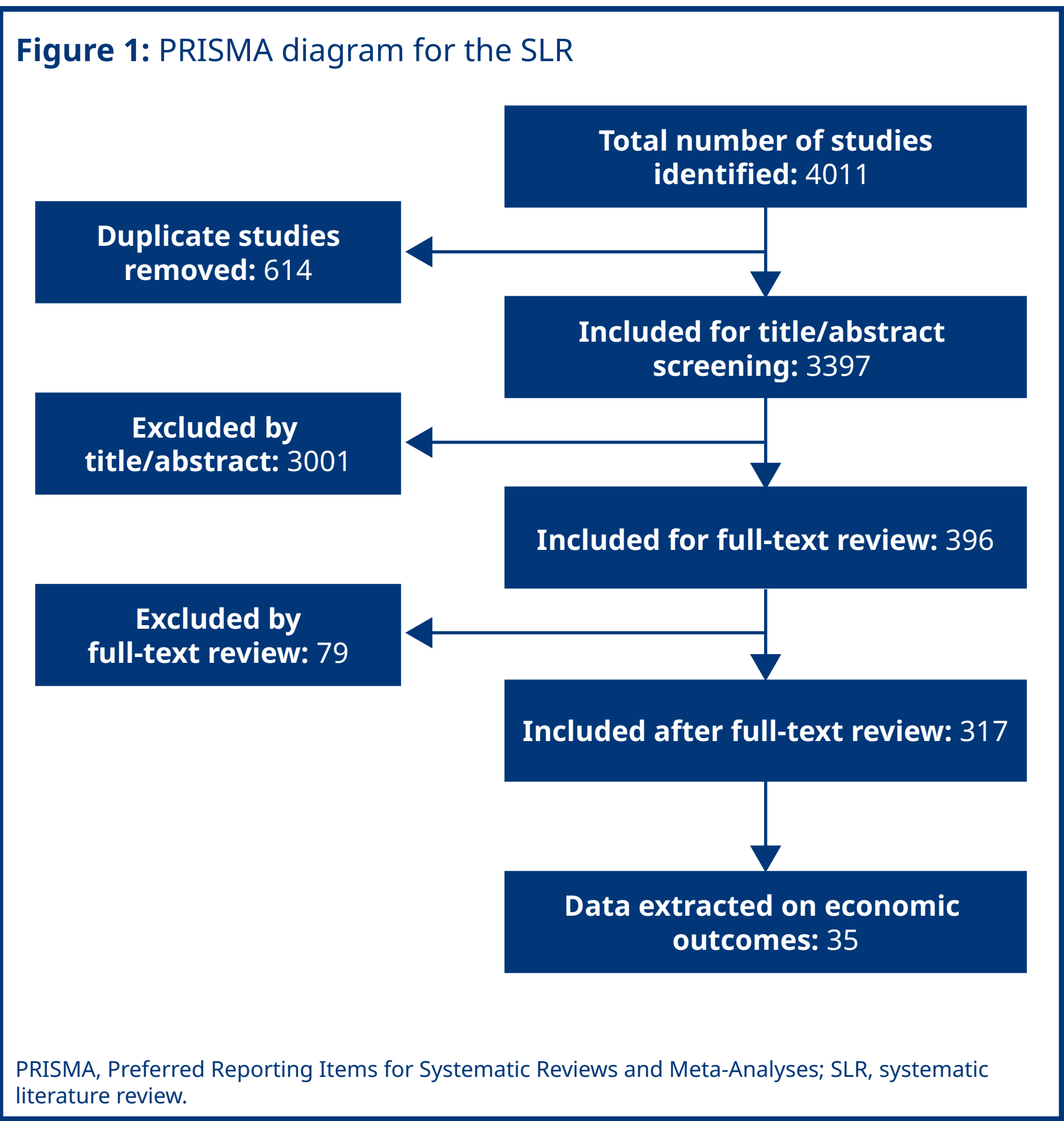


Table 2: Annual inpatient and outpatient healthcare costs by cirrhosis type in MASH

| Study, country (time period)                       | Data source                                | Cost type  | Cirrhosis type (number of patients) | PPPY costs  | Cost ratio (decompensated: compensated) |
|--|--|------------|-------------------------------------|-------------|---|
| Canbay 2021, Germany (2011–2016) <sup>9</sup>      | InGef research database                    | Inpatient  | Compensated (411)                   | EUR 6373    | 2.8                                     |
|  |  |            | Decompensated (20,614)              | EUR 17,985  |   |
|  |  | Outpatient | Compensated (411)                   | EUR 1362    | 1.2                                     |
|  |  |            | Decompensated (20,614)              | EUR 1587    |   |
| Romero-Gomez 2020, Spain (2006–2017) <sup>10</sup> | Hospital discharge records (CMBD database) | Inpatient  | Compensated (139)                   | EUR 2972    | 1.1                                     |
|  |  |            | Decompensated (2028)                | EUR 3181    |   |
|  |  | Outpatient | Compensated (139)                   | EUR 1343    | 1.2                                     |
|  |  |            | Decompensated (2028)                | EUR 1601    |   |
| Gordon 2020, USA (2007–2015) <sup>8</sup>          | Medicare 20% sample dataset                | Inpatient  | Compensated (3454)                  | USD 8221    | 4.7                                     |
|  |  |            | Decompensated (65,926)              | USD 38,916  |   |
|  |  | Outpatient | Compensated (3454)                  | USD 7685    | 2.3                                     |
|  |  |            | Decompensated (65,926)              | USD 17,843  |   |
| Wong 2021, USA (2006–2016) <sup>11</sup>           | Commercial claims database (MarketScan)    | Inpatient  | Compensated (7665)                  | USD 10,306  | 12.7                                    |
|  |  |            | Decompensated (15,833)              | USD 130,862 |   |
|  |  | Outpatient | Compensated (7665)                  | USD 20,207  | 2.1                                     |
|  |  |            | Decompensated (15,833)              | USD 43,374  |   |

CMBD, Conjunto Mínimo Básico de Datos; EUR, euro; InGef, German Institut für angewandte Gesundheitsforschung; MASH, metabolic dysfunction-associated steatohepatitis; PPPY, per person per year; USD, United States dollar.

Table 3: Studies reporting longitudinal all-cause or total healthcare cost data in MASH with cirrhosis

| Study, country (time period)                       | Data source  | Cost type (frequency)         | Cirrhosis type (number of patients) | Per-person costs before MASH diagnosis | Per-person costs after MASH diagnosis |
|--|--|-------------------------------|-------------------------------------|--|---------------------------------------|
| Romero-Gomez 2020, Spain (2006–2017) <sup>10</sup> | Hospital discharge records (CMBD database)             | Total healthcare (monthly)    | Compensated (139)                   | EUR 3738                               | EUR 5414                              |
|  |  |                               | Decompensated (2028)                | EUR 4866                               | EUR 7053                              |
| Petta 2020, Italy (2011–2017) <sup>12</sup>        | Administrative databases of Italian local health units | All-cause healthcare (annual) | Compensated (131)                   | EUR 10,629                             | EUR 19,681                            |
|  |  |                               | Decompensated (303)                 | EUR 7815                               | EUR 19,808                            |
| Wong 2021, USA (2006–2016) <sup>11</sup>           | Commercial claims database (MarketScan)                | Total healthcare (annual)     | Compensated (7665)                  | USD 25,720                             | USD 35,715                            |
|  |  |                               | Decompensated (15,833)              | USD 70,030                             | USD 181,134                           |

CMBD, Conjunto Mínimo Básico de Datos; EUR, euro; MASH, metabolic dysfunction-associated steatohepatitis; USD, United States dollar.

## Results

- Of the 3397 studies included for screening by title and abstract, 396 met the inclusion criteria for full-text review (**Figure 1**).
- A total of 317 publications were eligible after full-text review and data were extracted from 95 prioritized publications.
- In total, 35 studies, with a combined sample size of approximately 820,000 patients, reported data on economic outcomes.
  - Most studies were observational (34 studies) and retrospective (28 studies) in nature, and reported economic data from Canada and the USA (21 studies).

### Direct healthcare costs

- Two studies reported greater annual total healthcare costs for MASH with cirrhosis than MASH without cirrhosis.
  - In Denmark, mean total healthcare costs in the year leading up to MASH diagnosis were 1.5-fold higher for patients with cirrhosis than without cirrhosis.<sup>7</sup>
  - In the USA, mean total annual healthcare costs were 1.3-fold and 2.7-fold higher for people living with compensated cirrhosis and decompensated cirrhosis, respectively, compared with people living with MASLD/MASH without progression to cirrhosis.<sup>8</sup>
- Across four studies (n=116,070), inpatient costs were 1.1–12.7-fold higher for patients with decompensated cirrhosis than for those with compensated cirrhosis, and outpatient costs were 1.2–2.3-fold higher (**Table 2**).<sup>8-11</sup>
- In one study based in the USA (n=69,380), patients with decompensated cirrhosis had more healthcare interactions annually than those with compensated cirrhosis who, in turn, had more interactions than patients with MASH without cirrhosis (interactions, mean: 59.8 vs 37.3 vs 32.1).<sup>8</sup>
- Three studies reported increases in annual or monthly per-person all-cause or total healthcare costs following a diagnosis of MASH with compensated or decompensated cirrhosis (**Table 3**).<sup>9,12</sup>
  - In addition, two studies that reported data on outpatient and inpatient costs found that these costs increased after a diagnosis of MASH with compensated or decompensated cirrhosis.<sup>9,13</sup>
- Patient characteristics linked to cost differences in MASH with cirrhosis included age, ethnicity and fibrosis-4 index (FIB-4) score in studies based in the USA.
  - Total healthcare costs per person per year for patients with cirrhosis due to MASH were greater in older age groups, ranging from United States dollar (USD) 63,079 for those aged ≤44 years to USD 117,194 for those aged ≥65 years.<sup>14</sup>
  - Mean annual total hospital costs from 2016 to 2018 were significantly higher for Black individuals than for White individuals (USD 21,010 vs USD 17,677).<sup>15</sup>

- Total and inpatient costs were 10–20% higher when comparing patients with a FIB-4 score >4.12 with the partially overlapping population of patients with a FIB-4 score >3.5.<sup>16</sup>

### Indirect healthcare costs

- One study (n=1142) reported indirect costs in Denmark; compared with individuals without MASH, patients with MASH, with and without cirrhosis, were 7.2 and 4.4 times more likely to receive disability insurance, respectively.<sup>7</sup>

## Strengths and limitations

- To our knowledge, this is the first SLR to assess a broad range of outcomes in the specific subgroup of patients with cirrhosis due to MASH.
- We included studies based on the reporting of relevant outcomes in patients with cirrhosis due to MASH, regardless of how this was defined in each study; however, the definition of MASH varies in clinical practice owing to disease heterogeneity, low levels of awareness of risk factors among clinicians, and variation in the use of invasive and non-invasive diagnostic techniques.<sup>17,18</sup> This may have contributed to the observed heterogeneity in outcomes.

## Conclusions

- This SLR suggests that total healthcare costs in MASH can be more than 2.5 times higher for those with cirrhosis than for those without.
- Healthcare costs were generally higher for decompensated cirrhosis than compensated cirrhosis; inpatient costs, in particular, were up to 12 times higher for decompensated cirrhosis than compensated cirrhosis.
- Few data were identified on the indirect economic burden, the costs of informal or formal care, and the relationship between non-invasive test scores and healthcare costs.
- In addition to highlighting areas of unmet need, such as the timely treatment of earlier fibrosis stages, a better understanding of the burden associated with cirrhosis due to MASH could help to inform cost-benefit analyses of existing and future interventions.

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