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Original Article

ERCP Timing in Gallstone Disease: A Meta-Analysis of One-Stage versus Two-Stage Strategies

Mohamed Gamal[1, †], Mohamed Wagdy[2, †,*], Mahmoud Abd El-Nasser[3], Abdalla Ahmed Mohamed[4], Abdulrahman Waleed[3], Abdulrahman Ziada[5], Abdelrahman Abdalla Mohamed[4]

1-Faculty of Medicine, Assiut University, Assiut, Egypt
2-Faculty of Medicine, Modern University for Technology and Information, Cairo, Egypt
3-Faculty of Medicine, Kafr El-Sheikh University, Kafr El-Sheikh, Egypt
4-Faculty of Medicine, October 6 University, Giza, Egypt
5-Faculty of Medicine, Tanta University, Tanta, Egypt

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ABSTRACT

Background: Cholecystocholedocholithiasis involves gallbladder and bile duct stones. Standard two-stage care involves ERCP followed by cholecystectomy, whereas single-stage intraoperative ERCP may streamline treatment. We performed a meta-analysis comparing stone clearance, complications, and hospital stay between single-stage and two-stage strategies.
Method: We systematically searched PubMed, Scopus, Web of Science, and the Cochrane Library up to April 2025 for clinical studies comparing one-stage laparo-endoscopic rendezvous with two-stage ERCP + LC. RCTs and observational studies reporting stone clearance, complications, conversion, bile leaks, hospital stay, repeat ERCP, or cannulation failure were included. Data extraction and ROB2/NOS assessments were done independently.
Results: Twenty-four studies met the inclusion criteria. The one-stage approach demonstrated significantly higher CBD clearance (96.5% vs. 91.8%; RR = 1.03) and a notably lower overall complication rate (11.55% vs. 19.56%; RR = 0.51). Postoperative pancreatitis (RR = 0.50), cholangitis (RR = 0.33), and bleeding (RR = 0.47) were also significantly reduced. Although conversion to open surgery and bile leak rates were lower in the one-stage group, these differences were not statistically significant. Importantly, single-stage management resulted in shorter hospital stays (mean difference = 3.23 days), fewer postoperative repeat ERCPs (RR = 0.21), and markedly reduced cannulation failure (RR = 0.26).
Conclusion: The one-stage approach for managing bile duct stones offers higher clearance rates, fewer complications, and shorter hospital stays compared to the two-stage approach. These results support adopting one-stage treatment as a more effective and efficient clinical strategy.

1. Introduction

The simultaneous presence of gallbladder and common bile duct (CBD) stones, termed cholecystocholedocholithiasis, represents a clinically significant condition. Common bile duct stones (CBDS) are reported in approximately 8%–20% of patients with gallstones; however, the actual incidence is likely higher, as asymptomatic or undiagnosed cases are common. [1, 2]. The association of these two conditions can lead to many severe complications, such as acute biliary pancreatitis, jaundice, and cholangitis, transforming the choice of the best strategy for treating a benign issue into a potentially life-threatening problem. While the gold standard of treatment for gallstones has been laparoscopic cholecystectomy (LC) since the early 1990s, ERCP is considered optimal for isolated CBDS [3]. The optimal management of cholecystocholedocholithiasis remains debated [4, 5].

Historically, open surgery (choledochotomy with papillotomy) for common bile duct (CBD) stone removal was common but had high risks and is now rarely used, reserved for special cases where minimally invasive methods fail or are unavailable [6]. Preoperative ERCP followed by laparoscopic cholecystectomy is the most common current approach [7]. However, it's invasive, requires two procedures with separate anesthesia sessions, and can create scheduling issues in busy hospitals. Postoperative ERCP is used selectively when CBD stones are unexpectedly found during or after LC, especially when trained personnel or equipment are not immediately available [8]. While less invasive initially, it also requires a second anesthesia session and carries the risk of incomplete stone removal.

Intraoperative ERCP with concomitant laparoscopic cholecystectomy is a single-stage laparoendoscopic treatment. These single-stage laparoendoscopic approaches include primarily intraoperative ERCP, the laparoendoscopic rendezvous (LERV) technique (which was first described almost 20 years ago) [9], and transcystic

* Corresponding author: Mohamed Wagdy, Faculty of Medicine, Modern University for Technology and Information, Cairo, Egypt. Email: tamerwagdyali79@gmail.com

† These authors contributed equally to this work

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clearance. Compared to the classical two-stage approach of pre-ERCP for CBD stone removal followed by LC, performing LC concurrently with intraoperative ERCP alleviates pain, saving medical resources and costs by addressing two issues in a single procedure. Some studies also showed that the Single-stage Technique can reduce certain complications, such as post-operative pancreatitis and cholangitis [10, 11].

Our meta-analysis aims to evaluate whether the single-stage technique offers benefits over traditional two-stage approaches in terms of CBD stone clearance rates, procedure-related complications, and hospital stay duration in patients with concurrent gallbladder and CBD stones.

2. Methods

2.1. Search Strategy

PubMed, Scopus, Web of Science, and Cochrane Library were searched up to April 2025 for relevant published clinical studies using the following keywords (Gallstone Disease/ Common Bile Duct /Laparoscopic Cholecystectomy/ Celioscopic Cholecystectomy / Endoscopic Retrograde Cholangiopancreatography / LERV). Detailed search strategies for each database were provided in our **(supplementary files)**, **(Table 1)**.

2.2. Selection Criteria

All clinical studies, randomized controlled trials (RCTs), retrospective, prospective, and case-control studies published up to April 2025 that met the following criteria were included in our in our review: (1) comparing one-stage versus two-stage management for concomitant gallbladder with CBD stones studies; (2) reporting at least one of the following outcomes, such as CBD clearance rate, Overall Complication Rate, Post-operative Pancreatitis (PEP), Post-operative Cholangitis, Post-operative Bleeding, Operation Conversion Rate, Bile Leak rate, Length of Hospital Stay, Postoperative second ERCP rate, and cannulation failure rate; and (3) no language restriction for the included studies. Studies comparing laparoscopic CBD exploration (LCBDE) with one or two-stage management were excluded

2.3. Outcomes

1. The primary outcome of this analysis was the success rate of common bile duct (CBD) clearance.
2. Secondary outcomes will be categorized as follows: (1) Safety outcomes, including postoperative pancreatitis, cholangitis, bleeding, bile leak, and overall complication rate; (2) Technical outcomes, such as cannulation failure, conversion rate, and need for second ERCP; and (3) Recovery outcomes, measured by length of hospital stay.

2.4. Data Extraction

An Excel sheet for data extraction was designed. After that, it was accessible to all authors. All authors participated in data extraction. Extracted data for each study included: study ID (last name of first author and the publication year), country, study design, study groups, sample size, age, common bile duct diameter, outcome measures, and key findings.

2.5. Quality Assessment

Two reviewers independently performed quality assessment. A third reviewer was involved in the discussion to reach a consensus. We used the Cochrane risk of bias-2 (ROB 2) tool to assess the risk of bias in the included RCTs [12]. Additionally, we used the Newcastle–Ottawa Scale (NOS) to assess the risk of bias in the included observational studies [13]. **(Table 2)**

2.6. Statistical Analysis

Statistical analysis and all plots were conducted using R (v.4.4.3 for Windows) and the Meta package. Weighted mean differences were used for continuous data, and risk ratios were used for dichotomous data, with 95% confidence intervals (CIs). A p-value < 0.05 was considered statistically significant, determined by the Z test. Heterogeneity was evaluated using Cochran's Q test ($p < 0.1$); inconsistency across studies was quantified using the I2 statistic. Significant heterogeneity was defined as $I2 > 50\%$, in which case a random-effects model was used for pooling; otherwise, we performed continuity correction, i.e., added 0.5 and a proportional amount to groups when zero events were reported in each group, so they could be estimated and included in our meta-analysis.

Some studies reported continuous data as median and range. To solve this problem, we assumed the median was equal to the mean and estimated the SD as one-quarter of the range between the upper and lower limits, using Hozo's method [14]. A sensitivity analysis was conducted to assess the robustness of the pooled results. Publication bias was explored using funnel plots and quantified using the Egger test [15].

3. Results

3.1. Study Characteristics

Twenty-four studies compared one-stage (intraoperative ERCP + cholecystectomy) and two-stage (preoperative ERCP + cholecystectomy) approaches for common bile duct (CBD) clearance, reporting outcomes such as CBD diameter, postoperative complications (e.g., pancreatitis, bleeding), and hospital stay duration, with baseline patient ages typically ranging from 45 to 70 years, between 1999 and 2025, conducted across multiple centers.

3.2. Primary outcome

3.2.1. Success Rate of CBD Clearance

The CBD clearance rate was reported in 21 studies, with an incidence of 1379 of 1429 (96.50%) in the one-stage group and 1451 of 1580 (91.84%) in the two-stage group. The meta-analysis demonstrated that one-stage management achieved a significantly higher CBD clearance rate compared to the two-stage approach (RR: 1.03, 95% CI [1.01, 1.04], $p = 0.0021$), with moderate heterogeneity among studies ($I^2 = 43.1\%$, $\tau^2 = 0.0002$, $p = 0.0193$) **(Supplementary Figure 3)**. After omitting Garbarini–2017, the results remained consistent (RR: 1.02, 95% CI [1.00, 1.03], $I^2 = 29.7\%$) **(Supplementary Figure 13)**.

Subgroup analysis by study design (RCTs vs. retrospective studies) was performed to explore sources of heterogeneity and assess consistency of effects. The pooled analysis of randomized controlled trials (RCTs) showed no statistically significant difference between the one-stage and two-stage approaches (RR: 1.03, 95% CI [0.99, 1.07], $p = 0.0596$; $I^2 = 46.6\%$), whereas retrospective studies demonstrated a statistically significant advantage for the one-stage approach (RR: 1.03, 95% CI [1.01, 1.05], $p = 0.0435$; $I^2 = 45.4\%$). Although the RCT subgroup showed a statistically insignificant effect while the retrospective subgroup did show significance, the test for subgroup differences was not significant ($p = 0.98$). This indicates that the effect sizes of the two subgroups were statistically similar, and the apparent difference in significance is likely attributable to variations in sample size or statistical power rather than a true difference in effect. Therefore, both study designs consistently support a modest benefit of the one-stage approach in achieving higher CBD clearance rates **(Supplementary Figure 18)**.

3.3. Secondary outcome

3.3.1. Overall Complication Rate

The overall complication rate was reported in 16 studies, with incidences of 140 of 1212 (11.55%) in the one-stage group and 255 of 1304 (19.56%) in the two-stage group. The pooled analysis demonstrated that the one-stage approach was associated with a significantly lower overall complication rate compared with the two-stage strategy (RR: 0.51, 95% CI [0.36–0.72], p = 0.0002), with moderate heterogeneity among studies (I^2 = 61.4%, τ^2 = 0.2313, p = 0.0007) **(Supplementary Figure 4)**. Sensitivity analysis by omitting Gerosa et al. (2024) reduced heterogeneity and yielded consistent results (RR: 0.47, 95% CI [0.36–0.62], I^2 = 32.6%) **(Supplementary Figure 14)**.

Subgroup analysis by study design revealed that randomized controlled trials (RCTs) significantly favored the one-stage approach, showing a marked reduction in complications (RR: 0.62, 95% CI [0.46–0.83], I^2 = 4.9%). Similarly, retrospective studies also demonstrated a significant benefit (RR: 0.45, 95% CI [0.25–0.78]), although with higher heterogeneity (I^2 = 75.4%). Although the RCT subgroup showed lower heterogeneity, the retrospective subgroup exhibited greater variability, yet the test for subgroup differences was not statistically significant (p = 0.98). This indicates that the observed difference in statistical significance between subgroups is likely due to variations in sample size or study power rather than a true difference in effect size. Therefore, both study designs consistently support the conclusion that the one-stage approach substantially reduces the overall complication rate compared with the two-stage strategy **(Supplementary Figure 21)**.

3.3.2. Postoperative Pancreatitis

Postoperative pancreatitis was reported in 21 studies, with an incidence of 54 of 1453 (3.7%) in the one-stage group and 135 of 1702 (7.9%) in the two-stage group. The pooled meta-analysis demonstrated that the one-stage approach was associated with a statistically significant reduction in postoperative pancreatitis compared with the two-stage strategy (RR: 0.51, 95% CI [0.34–0.77], p = 0.0014), with low heterogeneity among the included studies (I^2 = 15.6%, τ^2 = 0.1841, p = 0.2556) **(Supplementary Figure 5)**. After omitting Passi et al. (2017), the results remained consistent, and heterogeneity decreased further (RR: 0.45, 95% CI [0.32–0.64], I^2 = 7.7%) (Supplementary Figure 15).

Subgroup analysis by study design showed that randomized controlled trials (RCTs) favored the one-stage approach. However, the effect did not reach statistical significance (RR: 0.44, 95% CI [0.16–1.22], p = 0.12), with no observed heterogeneity (I^2 = 0%, p = 0.4671). Retrospective studies demonstrated a statistically significant reduction in postoperative pancreatitis with the one-stage strategy (RR: 0.53, 95% CI [0.33–0.83], p = 0.01), accompanied by low-to-moderate heterogeneity (I^2 = 31%, p = 0.1437). The test for subgroup differences was not significant (p = 0.76), indicating that both RCT and retrospective analyses yielded statistically similar effects.

3.3.3. Postoperative cholangitis

Outcomes of Postoperative cholangitis were reported in 10 studies, with an incidence of 4 of 623 (0.64%) in the one-stage group and 25 of 793 (3.15%) in the two-stage group. The meta-analysis demonstrated that the one-stage approach was associated with a statistically significant reduction in Postoperative cholangitis compared to the two-stage approach (RR: 0.35, 95% CI [0.14, 0.88], p = 0.0263), and there was no heterogeneity among the studies (I^2 = 0.0%, τ^2 = 0.1306, p = 0.6216) **(Supplementary Figure 6)**.

3.3.4. Postoperative bleeding

Postoperative bleeding outcomes were reported in 15 studies, with an incidence of 16 of 1045 (1.53%) in the one-stage group and 34 of 1151 (2.95%) in the two-stage group. The meta-analysis demonstrated that the one-stage approach was associated with a statistically significant reduction in Postoperative bleeding compared to the two-stage approach (RR: 0.47, 95% CI [0.27, 0.82], p = 0.0082), and there was no heterogeneity among the studies (I^2 = 0%, τ^2 = 0, p = 0.8829) **(Supplementary Figure 7)**.

3.3.5. Bile leak

Outcomes of Bile leak were reported in 9 studies, with an incidence of 14 of 801 (1.74%) in the one-stage group and 17 of 819 (2.07%) in the two-stage group. The meta-analysis demonstrated that the one-stage approach was associated with a statistically insignificant reduction in Bile leak compared to the two-stage approach (RR: 1.44, 95% CI [0.68, 3.02], p = 0.3630), and there was no heterogeneity among the studies (I^2 = 0.0%, τ^2 = 0.0868, p = 0.7754) **(Supplementary Figure 9)**.

3.4. Technical outcomes

3.4.1. Operation conversion rate

The conversion rate for the operation was reported in 12 studies, with an incidence of 26 of 821 (3.17%) in the one-stage group and 89 of 915 (9.73%) in the two-stage group. The meta-analysis demonstrated that the one-stage approach was associated with a statistically insignificant reduction in Operation conversion rate compared to the two-stage approach (RR: 0.56, 95% CI [0.30, 1.04], p = 0.0649), and there was no significant heterogeneity among the studies (I^2 = 22.2%, τ^2 = 0.2223, p = 0.2257) **(Supplementary Figure 8)**. By omitting Raab 2024 (RR: 0.47, 95% CI [0.30, 1.04], I^2 =8.1%), **(Supplementary Figure 16)** .Subgroup analysis revealed that randomized controlled trials (RCTs) favored the one-stage strategy with a significant reduction in conversion (RR: 0.49, 95% CI [0.25, 0.96], p = 0.0445; I^2 = 26.6%), whereas retrospective studies demonstrated a non-significant effect (RR: 0.63, 95% CI [0.22–1.83], p = 0.2312; I^2 = 25.9%).confirming that the overall findings were robust and mainly driven by the RCT subgroup **(Supplementary Figure 20)**.

3.4.2. Postoperative second ERCP rate

Outcomes of Postoperative second ERCP were reported in 6 studies, with an incidence of 6 of 435 (1.38%) in the one-stage group and 30 of 365 (8.22%) in the two-stage group. The meta-analysis demonstrated that the one-stage approach was associated with a statistically significant reduction in Postoperative second ERCP compared to the two-stage approach (RR: 0.21, 95% CI [0.08, 0.58], p = 0.0026), and there was no heterogeneity among the studies (I^2 = 0.0%, τ^2 = 0.2894, p = 0.4846) **(Supplementary Figure 11)**.

3.4.3. Cannulation failure rate

Cannulation failure rate was reported in 12 studies, with an incidence of 8 of 828 (0.97%) in the one-stage group and 44 of 761 (5.78%) in the two-stage group. The meta-analysis demonstrated that the one-stage approach was associated with a statistically significant reduction in cannulation failure rate compared to the two-stage approach (RR: 0.26, 95% CI [0.14, 0.51], p < 0.0001), and there was no heterogeneity among the studies (I^2 = 0.0%, τ^2 = 0, p = 0.8979) **(Supplementary Figure 12)**.

Table 1: The baseline characteristics of our included studies

Study ID	Country + Year	Study Type	Group	Sample Size	Age (years)	CBD diameter (mm)	NOS
ElGeidie et al. [16]	Egypt 2011	RCT	One-stage	98	31.2 (20–67)*	9.6 (8–18)*	-
			Two-stage	100	27.5 (19–64)*	9.2 (7–20)*	
González et al. [17]	Cuba 2016	RCT	One-stage	99	58.4 (23–87)*	8.2 (4–20)*	-
			Two-stage	100	57.7 (20–84)	8.4 (5–12)*	
Lella et al. [18]	Italy 2006	RCT	One-stage	60	54.2 (22–60)*	NR	-
			Two-stage	60	54.2 (22–60)*	NR	
Morino et al. [19]	Italy 2006	RCT	One-stage	46	56.6 (22–82)*	CBD 10 mm = 60.8%	-
			Two-stage	45	63.1 (25–83)*	CBD 10 mm = 64.4%	
Muhammedoğlu et al. [20]	Turkey 2020	RCT	One-stage	39	60.5 (median)	12 (median)	-
			Two-stage	80	60.5 (median)	11 (median)	
Rabago et al. [21]	Spain 2006	RCT	One-stage	59	NR	NR	-
			Two-stage	64	NR	NR	
Sahoo et al. [22]	India 2014	RCT	One-stage	42	NR	NR	-
			Two-stage	41	NR	NR	
Tzovaras et al. [23]	Greece 2012	RCT	One-stage	50	66 (22–87)**	9 (4–20)**	-
			Two-stage	49	69 (25–85)**	9 (4–21)**	
Liu et al. [24]	China 2017	RCT	One-stage	32	42 (5.2)***	NR	-
			Two-stage	31	40 (6.1)***	NR	
Farid et al. [25]	Egypt 2024	RCT	One-stage	218	37.50 (25–60)**	NR	-
			Two-stage	218	42.50 (18–65)**	NR	
Garbarini et al. [26]	Italy 2016	Retrospective	One-stage	143	59 (16–88)*	NR	9
			Two-stage	106	68 (23–88)*	NR	
Greca et al. [11]	Italy 2007	Retrospective	One-stage	19	54 (9–88)*	NR	9
			Two-stage	19	52 (25–84)*	NR	
Jiang et al. [27]	China 2019	Retrospective	One-stage	22	56.5 (9.8)***	8.5 (6.2)***	7
			Two-stage	29	62.2 (10.4)***	7.8 (2.9)***	
Meyer et al. [28]	France 1999	Retrospective	One-stage	30	57 (28–84)*	NR	6
			Two-stage	203	56 (18–91)*	NR	
Muhammedoğlu et al. [29]	Turkey 2019	Retrospective	One-stage	31	61.29 (19.9)***	NR	8
			Two-stage	25	53.6 (18.1)***	NR	
Passi et al. [30]	America 2017	Retrospective	One-stage	37	41.1 (26.5)***	6.1 (4.7)***	9
			Two-stage	177	53.5 (21.2)***	8.6 (5.1)***	
Qian et al. [31]	China 2019	Retrospective	One-stage	123	56.3 (15.5)**	6.8 (2–14)**	9
			Two-stage	137	58.2 (16.0)**	7.2 (0.8–15)**	
Gerosa et al. [32]	Italy 2024	Retrospective	One-stage	105	72 (36–86)**	NR	9
			Two-stage	85	70 (41–78)**	NR	
Di Lascia et al. [33]	Italy 2021	Retrospective	One-stage	20	58 (30–80)**	NR	9
			Two-stage	20	64 (45–85)**	NR	
Mohamed et al. [34]	Egypt 2023	Retrospective	One-stage	100	41.56 (16.5)***	NR	8
			Two-stage	120	45.34 (13.6)***	NR	
Percario et al. [35]	Italy 2025	Retrospective	One-stage	120	NA	>10 mm	8
			Two-stage	70	NA	>10 mm	
Raab et al. [36]	Austria 2024	Retrospective	One-stage	103	62.6 (mean)	N/A	9
			Two-stage	66	63.8 (mean)	N/A	
Hu et al. [37]	China 2017	Retrospective	One-stage	28	51.0 (14.6)***	NR	7
			Two-stage	24	52.3 (12.9)***	NR	
Lv et al. [38]	China 2023	Case-control (Retrospective)	One-stage	40	60.5 (8.5)***	12.08 (2.25)***	8
			Two-stage	42	63.9 (11.6)***	12.86 (2.61)***	

*, Mean (range); **, median (range); ***, mean (standard deviation); NOS, Newcastle Ottawa scale for our retrospective studies

3.5. Recovery outcomes

3.5.1. Length of hospital stay

Outcomes of Length of hospital stay were reported in 20 studies, but many reported these outcomes as medians and ranges. We applied the Hozo et al. statistical method. The data was converted into a uniform format of means and standard deviations for analysis. The meta-analysis demonstrated that the one-stage approach was associated with a statistically significant shorter length of hospital stay compared to the two-stage approach (MD: -3.23, 95% CI [-4.23, -2.23], $p < 0.0001$), and there was a significant heterogeneity among the studies ($I^2 = 93.3\%$, $p < 0.0001$) **(Supplementary Figure 10)**. RCT subgroup: The pooled analysis of RCTs demonstrated that one-stage management significantly reduced the length of hospital stay compared to the two-stage approach (MD: –3.07 days, 95% CI [–4.43, –1.72], $p < 0.0001$), with very high heterogeneity ($I^2 = 91.8\%$, $\tau^2 = 3.5022$, $p < 0.0001$). Retrospective subgroup: Similarly, retrospective studies confirmed a significant reduction in hospital stay with one-stage treatment (MD: –3.45 days, 95% CI [–4.89, –2.02], $p < 0.0001$), again with considerable heterogeneity

Table 2: Quality assessment of included studies using the Newcastle-Ottawa Scale (NOS)

Study ID	S1	S2	S3	S4	C1	C2	O1	O2	O3	Total
Garbarini et al. [26]	*	*	*	*	*	*	*	*	*	9/9
Gerosa et al. [32]	*	*	*	*	*		*	*	*	8/9
Hu et al. [37]	*	*	*	*	*		*	*		7/9
Di Lascia et al. [33]	*	*	*	*	*	*	*	*	*	9/9
Lv et al. [38]	*		*	*	*		*	*	*	8/9
Meyer et al. [28]	*	*	*	*	*		*			6/9
Muhammedoğlu et al. [29]	*	*	*	*	*		*	*	*	8/9
Passi et al. [30]	*	*	*	*	*	*	*	*	*	9/9
Qian et al. [31]	*	*	*	*	*	*	*	*	*	9/9
Percario et al. [35]	*	*	*	*	*		*	*		8/9
Raab et al. [36]	*	*	*	*	*	*	*	*	*	9/9
Jiang et al. [27]	*	*	*	*	*		*	*		7/9
Greca et al. [11]	*	*	*	*	*	*	*	*	*	9/9
Mohamed et al. [34]	*	*	*	*	*		*	*	*	8/9

*, Mean (range); NOS, Newcastle Ottawa scale

($I^2 = 94.5\%$, $\tau^2 = 6.0386$, $p < 0.0001$). Both favored the one-stage approach to reducing hospital stay **(Supplementary Figure 19)**. We conducted leave-one-out analyses to address heterogeneity across studies and assess the strength of the results. The leave-one-out meta-analysis showed no significant difference in heterogeneity in the Length of hospital stay. Omitting the study by Hu (2017) shifts the mean difference to MD: -3.45 [-4.38; -2.51] and reduces heterogeneity to 86.2%, suggesting it may contribute disproportionately to the variability **(Supplementary Figure 17)**.

3.6. Publication bias

A funnel plot was constructed to assess the potential for publication bias among the included studies. In the plot, the effect estimates were symmetrically distributed around the pooled effect size, suggesting a low likelihood of publication bias. A slight asymmetry was observed, which may be attributable to heterogeneity or small-study effects rather than true bias. Visual inspection of the funnel plot did not reveal significant gaps or clustering that would indicate missing studies on one side of the plot. This interpretation was supported by Egger's regression test, which yielded a p-value of 0.24, indicating no significant effects. The result of Egger's test ($t = -1.22$, $p = 0.2401$) suggests that there is no statistically significant funnel plot asymmetry, implying no strong evidence of publication bias in the included studies.

3.7. Certainty of Evidence

The evidence suggests that one-stage procedures for common bile duct clearance have a slightly higher success rate than two-stage approaches. Randomized trials show a small advantage, though the confidence in this finding is only moderate because the results are somewhat uncertain. Non-randomized studies also point to a similar benefit but offer low certainty due to their study design. Across all studies, there were no major concerns about bias or inconsistency, and the overall direction of the findings was consistent. In summary, one-stage procedures appear to be somewhat more effective, but the confidence in this conclusion remains cautious because of methodological limitations and imprecision in the available evidence

4. Discussion

Endoscopic Retrograde Cholangiopancreatography (ERCP) remains a cornerstone in the management of choledocholithiasis and other biliary tract disorders. Still, it has several limitation due to high risk of pancreatitis, bleeding, and perforation even not success in all patient our study show 24 studies with a total 5,728 patients, with 2,881 patients (50.3%) in the one-stage group (intraoperative ERCP and laparoscopic cholecystectomy) and 2,847 patients (49.7%) in the two-stage group (preoperative ERCP followed by cholecystectomy).patients, demonstrates that one-stage management for choledocholithiasis is associated with superior clinical outcomes compared to the traditional two-stage approach. One-stage procedures yielded a significantly higher common bile duct (CBD) clearance rate (96.5% vs. 91.8%) and notably lower overall complication rates (11.6% vs. 19.6%), including reduced incidences of postoperative pancreatitis, Cholangitis, and bleeding. However, reductions in bile leak and conversion rates did not reach statistical significance. Nonetheless, the one-stage approach demonstrated favorable trends overall and appears to be a safer and more effective strategy for managing choledocholithiasis in appropriately selected patients.

Although the one-stage approach requires close coordination between surgical and endoscopic teams, patients benefit from shorter hospital stays and fewer repeat ERCPs, largely because treatment is consolidated into a single procedure. This streamlined pathway reduces delays between interventions, minimizes repeated anesthesia exposure, and lowers the risk of interval complications—ultimately enhancing both clinical efficiency and patient outcomes. However, these advantages must be weighed against higher initial setup costs and the need for specialized equipment and training.

Comparison with current guidelines. Our meta-analysis demonstrating higher CBD clearance, fewer overall complications (notably lower rates of post-ERCP pancreatitis), fewer repeat ERCPs, reduced cannulation failure, and shorter hospital stay with one-stage (laparo-endoscopic rendezvous) management — aligns with

guideline authors who recognize potential advantages of single-session strategies in suitable patients and high-expertise centres. ESGE and ASGE guidance acknowledge that intraoperative rendezvous techniques may reduce the risk of procedural pancreatitis and improve technical success, but they continue to recommend that the choice of timing and technique (preoperative ERCP, intraoperative ERCP/rendezvous, or laparoscopic bile-duct exploration) be individualized based on patient presentation and local surgical/endoscopic expertise. In cases of suspected or confirmed acute cholangitis, the Tokyo Guidelines prioritize prompt biliary drainage based on severity. While our pooled data on the one-stage approach for cholangitis reduction are reassuring, severe cholangitis still mandates urgent decompression, and the timing/mode of drainage should follow established severity-based algorithms. Our findings support guideline positions that intraoperative rendezvous is an effective option and suggest that, where logistical and expertise barriers can be overcome, guidelines could more strongly endorse single-session management as a preferred strategy to reduce pancreatitis, repeat procedures, and hospital stay [39, 40].

Operator experience is a critical determinant of success in LERV procedures. High-volume centers with skilled surgical and endoscopic teams consistently report lower complication rates, reduced cannulation failures, shorter operative times, and higher rates of duct clearance.

Di Lascia et al. (2019) reported that a one-stage procedure was associated with longer operative times and required greater technical expertise [33].

Cuschieri et al. (1999) reported technical challenges with intraoperative ERCP and concluded that the two-stage approach remained a safer and more feasible option. These studies highlight that, despite the potential advantages of the one-stage approach, its success is highly dependent on institutional resources and operator experience [41].

Many studies strongly support our findings, demonstrating that the one-stage approach using the laparoscopic-endoscopic rendezvous (LERV) technique significantly reduced the incidence of post-ERCP pancreatitis and shortened hospital stays compared to the traditional two-stage method, with higher CBD clearance rates and lower overall complication rates [41, 42, 43].

Morino et al. (2006) reported that the LERV technique not only improved the success rate of bile duct stone removal but also reduced the need for additional procedures and facilitated faster patient recovery [19]. Similarly, Bozkurt et al. (2013) demonstrated that intraoperative ERCP combined with laparoscopic cholecystectomy achieved higher bile duct clearance rates and significantly fewer postoperative complications compared to the two-stage approach. This strategy was also associated with shorter hospital stays and a reduced need for repeat ERCPs, thereby enhancing both patient outcomes and healthcare efficiency [44].

However, past techniques or protocols present several challenges. It often necessitates two separate hospital admissions and anesthesia sessions, increasing overall costs and patient burden. Additionally, some stones may pass spontaneously before ERCP, rendering the procedure redundant in certain cases. A false-negative rate of 6.1% was observed, indicating that stones were occasionally missed. Moreover, the Inflammation sometimes mandates conversion to open surgery. Failure of the ERCP procedure itself sometimes necessitated an additional, third intervention to manage the bile duct stones or related complications, which increases patient risk.

4.1. Limitations

The present analysis included studies with mixed designs (randomized controlled trials and retrospective cohort studies). This inherent variation in study methodology may have introduced bias and heterogeneity, potentially affecting the reliability of the pooled estimates. In addition, several other limitations should be acknowledged. First, some of the included studies reported continuous variables as median and range, which required transformation into mean and standard deviation using Hozo's method. While this statistical approach is widely applied in meta-analyses, it introduces a degree of approximation and potential error, and thus, our pooled results should be interpreted with caution. Second, the studies spanned more than two decades (1999–2025) and were conducted across diverse healthcare systems. Advances in laparoscopic and endoscopic techniques, improvements in perioperative care, and variations in healthcare infrastructure and practice patterns over time and across regions may have contributed to heterogeneity and limited the generalizability of our findings. Third, although stone size and bile duct diameter are important determinants of clearance, only a limited number of studies reported these variables, and the data were expressed in heterogeneous formats (mean, median, or percentages). This inconsistency precluded subgroup or stratified analyses based on these clinically relevant factors. Fourth, although overall complication rates were consistently reported, most studies did not stratify complications by severity (e.g., using the Clavien–Dindo classification or distinguishing between major and minor complications). The lack of standardized complication reporting prevented a meaningful pooled analysis of morbidity profiles. Finally, while cost-effectiveness is an important consideration in the choice between one-stage and two-stage management, very few studies reported hospital resource utilization data, and no consistent cost-effectiveness data were available to allow pooled analysis of economic outcomes.

Future research directions

Future studies should aim to overcome these limitations by adopting standardized definitions and classification systems for complications (such as the Clavien–Dindo grading), consistently reporting bile duct diameter and stone characteristics, and including comprehensive cost-effectiveness analyses. Moreover, well-designed, contemporary randomized controlled trials conducted across diverse healthcare systems would provide more robust, generalized evidence to guide clinical practice. Mixed between randomized controlled trials and retrospective analyses, which may introduce heterogeneity and affect the strength of pooled conclusions. Also, differences in patient selection criteria, operator experience, and institutional protocols across studies could influence outcomes. And how studies address confounding variables encountered by physicians in assessing bile duct clearance or complication severity.

5. Conclusions

These findings have important implications for clinical practice and could influence future guideline recommendations for the management of choledocholithiasis. The demonstrated superiority of the one-stage approach in terms of CBD clearance, reduced complications, shorter hospital stays, and fewer repeat procedures supports its adoption as the preferred strategy. Current guidelines, which often present both one-stage and two-stage options, may benefit from more explicit recommendations favoring the one-stage approach

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research

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Authors' Contribution

MG contributed to conceptualization, project administration, and preparation of tables. AA, AWM, AA, and ZA performed screening, data extraction, and risk of bias assessment. MW conducted statistical analysis using R software, drafted the manuscript, and wrote the discussion section.

Data Availability

All data supporting the findings of this study are available within the article and its supplementary materials. No new datasets were generated.

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ASIDE

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Original Article

Fish-Bone Migration to the Liver Causing Hepatic Abscess: A Scoping Review of Published Cases (2015–2025)

Zaid Alezzi[1], Tarek Aboubakr[2], Ashraf Yahia Hegab[3], Abdulkarim Hasan [4,5,*]

1-Department of Gastroenterology, Mikhwa General Hospital, Al-Baha Health Cluster, Ministry of Health, Mikhwa, Saudi Arabia
2-Department of Intensive Care Unit, Prince Mishari bin Saud Hospital, Al-Baha Health Cluster, Ministry of Health, Baljurashi, Saudi Arabia
3-Department of Internal Medicine Prince Mishari bin Saud Hospital, Al-Baha Health Cluster, Ministry of Health Baljurashi, Saudi Arabia
4-Department of Pathology Prince Mishari bin Saud Hospital, Al-Baha Health Cluster, Ministry of Health, Baljurashi, Saudi Arabia
5-Department of Pathology, Faculty of Medicine Al-Azhar University, Cairo, Egypt

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ABSTRACT

Background: Foreign body ingestion is common; however, migration of an ingested fish bone into the liver with subsequent abscess formation is rare, frequently presents with nonspecific abdominal symptoms, and poses a diagnostic challenge in routine clinical practice, often leading to delayed diagnosis.
Methods: A scoping review of PubMed, Google Scholar, SciELO, and ScienceDirect identified human case reports and case series (2015–2025) describing confirmed intrahepatic fish-bone migration or penetration causing hepatic abscess. Reports without radiologic or intraoperative confirmation and those involving non–fish-bone foreign bodies were excluded. Extracted data included demographics, migration routes, imaging findings, management, and outcomes.
Results: Twenty-seven publications reporting 29 patients met the inclusion criteria, including 25 individual case reports and 2 case series. Presumed transgastric migration was reported in 22 patients (75.9%), and the left hepatic lobe was involved in 20 cases (69.0%). Computed tomography identified a linear radiodense foreign body in 24 patients (82.8%). Surgical or minimally invasive foreign-body removal was performed in 21 patients (72.4%), with generally favorable outcomes, although follow-up reporting was variable.
Conclusion: Intrahepatic fish-bone migration is a rare but clinically important cause of hepatic abscess and should be considered in patients with unexplained, particularly left-lobe, hepatic abscesses when CT demonstrates a linear foreign body or when response to standard therapy is atypical; timely source control is usually effective.

1. Introduction

Foreign-body migration from the gastrointestinal (GI) tract into the liver is a rare but clinically important cause of hepatic abscess. Because the available evidence consists almost exclusively of isolated case reports and small case series, the true prevalence of intrahepatic fish-bone migration cannot be reliably estimated. Most ingested foreign bodies pass spontaneously; however, sharp objects can perforate the stomach or duodenal wall and migrate into adjacent structures, including hepatic parenchyma, where they may act as a nidus for infection and abscess formation. Fish bones are frequently implicated because their thin, pointed shape increases the likelihood of mucosal injury and perforation, and ingestion is often unrecognized by patients [1].

This entity has been recognized for more than a century. The first description of a hepatic abscess resulting from GI perforation by an ingested foreign body is commonly attributed to Lambert (1898). Subsequent reports have reaffirmed this mechanism but emphasize that diagnosis is challenging because symptoms are non-specific and a history of ingestion is usually absent [1, 2]. With the broader availability of computed tomography (CT), preoperative recognition improved substantially: CT can demonstrate a linear hyperdense foreign body within or adjacent to a hepatic collection and may show inflammatory change along the stomach or duodenum, enabling earlier definitive management [3, 4].

In recent years, additional case reports have expanded the clinical spectrum of confirmed intrahepatic fish-bone migration, including variation in hepatic segment involvement and an increasing use of minimally invasive approaches, such as laparoscopy, for drainage and foreign-body extraction [5, 6]. However, these reports remain scattered and use heterogeneous terminology, which complicates comprehensive identification. Therefore, this review aims to synthesize all reported cases of confirmed intrahepatic fish-bone migration from 2015 to 2025, focusing on patient characteristics, suspected migration routes, imaging findings, management strategies, and outcomes [5, 6].

* Corresponding author: Abdulkarim Hasan, Department of Pathology, Faculty of Medicine Al-Azhar University Cairo, Egypt Email: doctorabdulkarim7@gmail.com

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2. Methods

2.1. Search strategy

A scoping review of published case reports and case series was conducted to identify patients with confirmed intrahepatic fish-bone migration causing hepatic abscess. Searches were performed in PubMed, SciELO, Google Scholar, and ScienceDirect for studies published between January 2015 and December 2025. The final searches were completed in December 2025 (exact database run dates were not retained).

In PubMed, the search was conducted in the Title/Abstract fields using the following Boolean strategy: (fish bone OR fishbone OR "foreign body") AND ("hepatic abscess" OR "liver abscess" OR "pyogenic liver abscess") AND (migration OR penetration OR perforation).

Filters applied: Humans; publication date 2015 – 2025.

In SciELO, the following Boolean strategy was used with the publication-year filter 2015 – 2025 (no language restrictions applied): (fish bone OR fishbone OR "foreign body") AND ("hepatic abscess" OR "liver abscess" OR "pyogenic liver abscess") AND (migration OR penetration OR perforation).

For Google Scholar and ScienceDirect, searches were performed using the query "fish bone liver abscess"; results were sorted by relevance, and the first 200 records from each platform were screened to apply a reproducible stopping rule. Reference lists of included articles were also manually screened to identify additional eligible reports.

2.2. Eligibility, study selection, and data extraction

Eligible studies were human case reports or case series (2015 – 2025) with radiologic and/or intraoperative confirmation of an intrahepatic fish bone, defined as the Strict A-only criterion. Studies involving non – fish-bone foreign bodies, extrahepatic collections, animal studies, or review articles without new patient-level data were excluded.

Study selection was conducted independently by two reviewers. Records were de-duplicated prior to screening, and disagreements were resolved by consensus. For Google Scholar and ScienceDirect, we applied a reproducible stopping rule. We screened the first 200 records from each platform (sorted by relevance), in addition to records retrieved from PubMed and SciELO, and any additional eligible reports identified through reference-list screening. To minimize duplicate patient inclusion across publications, we cross-checked potentially overlapping reports using institutional and authorship information, patient demographics, and clinical timelines; when duplication could not be excluded, the most complete report was retained. Because full cross-platform retrieval counts and duplicate counts were not retained at the time of the initial search, a complete stepwise flow count (identified → de-duplicated → screened → full-text assessed → excluded) cannot be reported with precision.

Data extracted included patient demographics, suspected migration route, hepatic location, imaging findings, management approach, and outcomes. Findings were summarized descriptively in **(Table 1)** without meta-analysis.

2.3. Quality appraisal

No formal quality appraisal was performed, consistent with the descriptive aim of this scoping review and the nature of the included evidence (case reports and case series).

3. Results

Using the predefined Strict A-only definition (radiologic and/or intraoperative confirmation of an intrahepatic fish bone), we identified 27 publications reporting 29 individual patients between 2015 and 2025. Two reports included more than one case (Tan et al. and Mateus et al.), whereas the remaining 25 publications reported single-patient case series. Inclusion criteria were case reports or case series describing intrahepatic fishbone foreign bodies with radiologic and/or intraoperative confirmation and sufficient patient-level clinical details. No age restrictions were applied. Studies were excluded primarily because they involved non – confirmed fish-bone foreign bodies, did not document an intrahepatic fish bone, lacked radiologic and/or intraoperative confirmation, or were review articles without new patient-level data.

Cases were reported across multiple regions, including Asia, Europe, North and South America, and Africa, indicating that intrahepatic fish-bone migration is a global phenomenon rather than a geographically restricted condition. The mean age was 56.8 years (median 57; range 17 – 80), with 17 males and 12 females (male-to-female ratio 1.4:1).

When the presumed route of migration was described, transgastric migration was reported in 22 of 29 patients (75.9%), most commonly from the antrum or lesser curvature, whereas transduodenal penetration occurred in 5 patients (17.2%); the route was unspecified in 2 patients (6.9%). Fistulous tracts (e.g., hepatogastric or duodenohepatic) were described in a minority of cases. The left hepatic lobe was involved in 20 patients (69.0%), including several cases affecting segment III. Right-lobe involvement was reported in 8 patients (27.6%), and caudate involvement in 1 patient (3.4%).

Diagnostic confirmation relied primarily on computed tomography (CT), which identified a linear radiodense foreign body within or contiguous with an intrahepatic collection in 24 patients (82.8%). Upper gastrointestinal endoscopy at initial presentation was reported in 9 patients (31.0%), with positive findings in 4 patients (44.4%), including mucosal ulceration, suspected penetration sites, or visualization of the foreign body.

Antibiotic therapy was administered in 27 patients (93.1%). Source control was achieved through interventional or surgical approaches. Initial interventional radiology – guided drainage was attempted in 6 patients (20.7%); however, 4 of these subsequently required surgical intervention. Definitive surgical management was performed in 21 patients (72.4%), most commonly abscess drainage with foreign-body removal via laparoscopic or open approaches; staged percutaneous strategies were rarely reported. In two reports, the foreign body was left in situ with clinical monitoring. Outcomes were reported as recovery in 25 patients (86.2%), while outcomes or follow-up details were not reported or unclear in 4 patients (13.8%).

4. Discussion

This scoping review summarizes published reports of confirmed intrahepatic fish-bone migration causing hepatic abscess between 2015 and 2025 **(Table 1)**. Across reported cases, several consistent patterns emerge: (1) patients often present with non-specific symptoms typical of pyogenic liver abscess, (2) the presumed route is most frequently trans-gastric, and (3) the foreign body is most commonly located in the left hepatic lobe/segment III, reflecting the close anatomic relationship between the stomach (especially the antrum/lesser curvature) and the left liver. These observations are repeatedly described in individual case reports and small case series throughout the study period [5–22].

Table 1: Summary of reported cases of confirmed intrahepatic fish-bone migration causing hepatic abscess (2015–2025).

Ref No	Study	Country	Patient	Route/perforation	Hepatic location	Proof fishbone in liver	Treatment	Outcome
[6]	Panebianco (2015)	Italy	57 F	Gastric wall (antrum)	Left lobe	CT + laparoscopic identification of fish bone in liver abscess	Laparoscopic drainage + fish bone removal	Recovered
[17]	Morelli (2015)	Italy	65 M	Trans-gastric migration	Left lobe	CT/intraop confirmation of fish bone in liver abscess	Drainage + foreign body removal (approach)	Recovered
[20]	Venkatesh (2015)	Singapore	69 M	Lesser curvature; gastrohepatic fistula	Left lobe	CT showed a fish bone traversing the stomach into a liver abscess	Drainage + antibiotics (definitive management)	Recovered
[12]	Ede (2015)	South Africa	61 M	GI perforation	Left lobe	Imaging + intraop fish bone identified in liver abscess	Surgical drainage + fish bone removal	Recovered
[23]	Peixoto (2016)	Portugal	80 F	Duodenohepatic fistula / GI penetration	Right lobe	CT showed intrahepatic fish bone associated with an abscess	Antibiotics + drainage + surgical management	Recovered
[19]	Tan (2016) – Case 1	Singapore	56 M	Gastric antrum	Left lobe	CT showed intrahepatic fish bone in an abscess	Percutaneous drainage + laparoscopic fish bone removal	Recovered
[19]	Tan (2016) – Case 2	Singapore	63 M	Stomach	Left lobe	CT showed intrahepatic fish bone in an abscess	Percutaneous drainage + laparoscopic fish bone removal	Recovered
[18]	Kfouri (2017)	Brazil	56 F	Gastric perforation	Segment III (left lobe)	CT showed a fish bone in the hepatic parenchyma	Left lateral segmentectomy + drainage	Recovered
[8]	Bandeira-de-Mello (2018)	Brazil	44 F	Lesser gastric curvature	Left lobe	CT confirmed a fish bone associated with an abscess	Laparoscopy with fish bone extraction	Recovered
[16]	Mateus (2018) – Case 1	Portugal	76 M	GI perforation	Left lobe	CT/intraop fish bone migration	Laparotomy + fish bone removal	Recovered
[16]	Mateus (2018) – Case 2	Portugal	45 M	GI perforation	Right lobe	CT suggested fish bone; migration	Drainage (percutaneous) ± antibiotics; fish bone management	Not reported
[21]	Yu (2018)	China	34 F	Stomach perforation	Left lobe	CT hyperdense linear foreign body within an abscess	Surgery + fish bone removal	Recovered
[10]	Bekki (2019)	Japan	51 M	Stomach wall	Left lobe (subcapsular/adjacent)	Laparoscopy found a fish bone in the liver abscess region	Laparoscopic drainage + fish bone removal	Recovered
[15]	Li (2019)	China	58 M	Stomach wall penetration	Liver	CT + minimally invasive operation confirmed a fishbone	Minimally invasive removal + drainage + antibiotics	Recovered
[5]	Chen (2019)	China	37 M	Transgastric; segment III inflammation	Segment III (left lobe)	CT + laparoscopy confirmed a migrated fish bone	Laparoscopic removal (± segmentectomy)	Recovered
[24]	Burkholder (2019)	USA	64 F	The stomach directly feeds into the liver	Left lobe	Imaging evidence of fish bone, attributed to perforation	Drainage + antibiotics; foreign body left in situ	

CT, Computed Tomography; GI, Gastrointestinal; 3D, Three-Dimensional; FB, Foreign Body; F, Female; M, Male.

Table 1: Summary of reported cases of confirmed intrahepatic fish-bone migration causing hepatic abscess (2015 – 2025).

Ref No	Study	Country	Patient	Route/perforation	Hepatic location	Proof fishbone in liver	Treatment	Outcome
[25]	Sim (2019)		56 F	Distal stomach	Liver	Imaging showed retained fish bone within the abscess	Removal of foreign body (approach)	Recovered
[26]	Hernández-Villafranca (2020)	Mexico	71 M	GI migration	Left lobe	CT showed a sharp foreign body protruding from the left lobe	Surgical management	Recovered
[9]	Barkai (2020)	Israel	66 F	Migrating from the stomach	Liver	CT/intraop confirmed fish bone	Laparoscopic retrieval + abscess drainage	Recovered
[13]	Silva (2021)	Portugal	70 F	Gastric perforation	Left lobe	CT identified a fish bone and a hepatic abscess	Surgical removal + drainage	Recovered
[14]	Grayson (2022)	UK	56 M	Hepatogastric fistula	Segment III (left lobe)	CT linear foreign body; laparoscopy retrieved a fish bone from the liver	Laparoscopic retrieval + fistula disconnection/closure	Recovered
[27]	Xia (2022)	China	17 M	Fishbone perforation	Caudate lobe	CT showed a fish bone; it was removed from the liver	3D laparoscopic partial caudate lobectomy + drainage + fishbone removal	Recovered
[11]	Dai (2023)	China	55 M	From the stomach to the liver	Liver	CT confirmed a fish bone penetrated the liver	Laparoscopic removal (early-stage)	Recovered
[28]	Okhotnikov (2024)	Russia	55 M	Migration from the upper GI	Left lobe	Abscess drainage tract used for visually controlled bone extraction	Two-stage percutaneous drainage + percutaneous endoscopic bone extraction	Recovered
[29]	Cuesta-Pertuz (2024)	Colombia	55 M	Migration from the GI tract	Liver	Imaging + clinical correlation; fish bone migration described	Drainage + foreign body management	Not reported
[30]	Khan (2025)	India	59 F	GI perforation	Liver	Fish bone-induced hepatic abscess described	Antibiotics + percutaneous drainage; foreign body left in situ	Not reported
[31]	Ahmed (2025)	Bangladesh	35 F	Lesser gastric curvature perforation	Segment III/IVb (left lobe)	Intraop found a fish bone within the resected liver segment	Hepatic resection + antibiotics	Recovered
[22]	Zong (2025)	China	77 F	Ingested fishbone; GI penetration	Liver	CT 3D reconstruction confirmed fishbone; removed	Laparoscopic incision/drainage + fishbone removal	Recovered
[7]	Abdennebi (2025)	Morocco	60 M	Migration through the GI wall (not recalled)	Left lobe	CT showed radiodense linear intrahepatic FB; extracted fishbone	Laparoscopic removal under intraoperative ultrasound	Recovered

CT, Computed Tomography; GI, Gastrointestinal; 3D, Three-Dimensional; FB, Foreign Body; F, Female; M, Male.

Because the evidence base is derived from published case reports/series, it is inherently subject to selection and reporting biases; therefore, findings should be interpreted as descriptive patterns rather than estimates of true prevalence or comparative effectiveness.

4.1. Pathophysiology and anatomic pattern

Fish bones are thin, sharp, and capable of occult mucosal penetration; after perforating the stomach or duodenum, they may traverse the lesser omentum/adjacent tissues and lodge within hepatic parenchyma, leading to localized inflammation and abscess formation. The predominance of left-lobe involvement in reported cases supports this mechanism because the left lobe lies adjacent to the stomach. In contrast, right-lobe and caudate involvement are less common and may reflect variable penetration sites, migration pathways, and delayed presentation [5, 6, 8, 10, 12, 15–21, 27].

4.2. Diagnostic implications: the key role of CT

A major practical message from the included literature is that computed tomography (CT) is central to diagnosis. The typical hallmark is a linear radiodense structure within or contiguous with an intrahepatic collection, sometimes with inflammatory changes at the gastric/duodenal wall or a visible tract/fistula. In many reports, CT either enabled a definitive preoperative diagnosis or prompted targeted surgical/interventional exploration that confirmed the presence of a foreign body [3–7, 9–15, 17, 19–22, 26, 27].

Because many patients do not recall ingestion, clinical suspicion should increase in left-lobe abscesses that are atypical, recurrent, or show incomplete response to antibiotics and drainage alone [6, 9, 12–15, 17, 20, 21, 24].

4.3. Diagnostic pitfalls (when CT may miss a fish bone)

Despite its central role, CT may fail to identify a fish bone when the object is very small, oriented parallel to the imaging plane, obscured by adjacent structures, or when slice thickness/technique limits conspicuity. When suspicion remains high despite an initially negative or equivocal CT, consideration may be given to targeted radiology re-review and/or repeat CT with thinner slices, particularly for refractory or atypical left-lobe abscesses [6, 9, 12–15, 17, 20, 21, 24].

4.4. Management strategies and evolving minimally invasive approaches

Reported management generally emphasizes antibiotics plus source control. Antibiotic therapy typically consists of broad-spectrum agents targeting enteric organisms, including third-generation cephalosporins, beta-lactam/beta-lactamase inhibitor combinations, or carbapenems, with subsequent adjustment based on microbiological data when available. Source control may include abscess drainage, foreign-body removal, and (when present) management of a fistula tract. Across recent cases, there is a clear shift toward minimally invasive strategies, particularly laparoscopy, often combined with drainage (percutaneous or surgical), depending on abscess size, location, and patient stability. Multiple reports describe successful laparoscopic drainage and extraction, including techniques aided by intraoperative ultrasound or advanced laparoscopic approaches for difficult locations [5–7, 9–11, 14, 19, 22, 27].

However, the included literature also shows that management must be individualized. Some cases required laparotomy or more extensive procedures, including hepatic resection/segmentectomy for deeply embedded foreign bodies, complex anatomy, or uncertainty regarding complete source control [16, 18, 27, 31]. In selected patients, pre-operative upper gastrointestinal endoscopy may assist in identifying mucosal defects, fistulous tracts, or retained foreign bodies and can inform procedural planning. A minority of reports describe staged or alternative strategies, such as percutaneous drainage with subsequent controlled extraction via a drainage tract, highlighting that interdisciplinary planning (surgery, interventional radiology, gastroenterology) can be beneficial, particularly for high-risk surgical candidates [28].

4.5. Practical decision pathway (derived from reported cases)

Based on the descriptive patterns in the included reports, a pragmatic approach may be as follows: initiate antibiotics and assess clinical stability; in stable patients with a drainable collection, consider percutaneous drainage while actively evaluating for a retained foreign body and tract/fistula; pursue early foreign-body removal (endoscopic or surgical, depending on location and feasibility) when imaging shows a foreign body, when drainage fails, or when sepsis persists; and consider fistula/tract evaluation (imaging and/or endoscopy) when there is recurrent abscess, persistent contamination, or evidence of communication on imaging [5–7, 9–11, 14, 19, 22, 27].

4.6. Special situations: fistulas and "foreign body left in situ."

A subset of reports describes fistulous communication (e.g., hepatogastric or duodenohepatic), which may require not only drainage and extraction but also tract disconnection/closure to prevent recurrence [14, 20, 23]. In contrast, at least one report described management with the foreign body left in situ under monitoring; this should be considered exceptional and generally reserved for situations where removal is judged high risk (e.g., proximity to major vascular/biliary structures, technically inaccessible location, or prohibitive operative risk) [24]. In such situations, conservative management should include close clinical follow-up, interval imaging to document abscess resolution and stability of the foreign body, and a low threshold for escalation if symptoms recur or inflammatory markers rise.

4.7. Limitations and evidence gaps

The evidence base remains dominated by single-case reports and small series with heterogeneous reporting of key variables (e.g., exact route, segment location, organisms, duration of follow-up). Publication bias is likely, as unusual or successfully treated cases are more often reported; language bias may also be present, as relevant cases may be published in languages not captured by the databases searched. Therefore, conclusions should be interpreted as descriptive patterns rather than comparative effectiveness evidence.

5. Conclusion

Confirmed intrahepatic fish-bone migration is an uncommon but clinically important cause of hepatic abscess. Across reported cases from 2015 – 2025, migration most often follows gastric penetration and preferentially involves the left hepatic lobe, consistent with anatomical proximity between the stomach and the liver. Computed tomography is the key diagnostic tool, with a typical finding of a linear radiodense foreign body within or contiguous with an intrahepatic collection. Because this scoping review synthesizes published case reports and small case series, findings should be interpreted as descriptive trends rather than estimates of prevalence or comparative effectiveness.

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research

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Ethical approval

None.

Large Language Model

The authors declare that generative artificial intelligence (AI) tools (ChatGPT, OpenAI) were used solely to assist with language refinement and grammar checking during preparation of this manuscript. These tools were not used for screening, study selection, data extraction, data analysis, or interpretation of findings. The authors reviewed and verified all content and take full responsibility for the integrity and accuracy of the manuscript.

Authors Contribution

All authors contributed to the manuscript design, literature review, writing, and revision.

Data Availability

This study is a scoping review of published literature. No new datasets were generated or analyzed. All data supporting the findings are contained within the included articles cited in the reference list and the summary extraction presented in Table 1.

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Review Article

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): A Multisystemic Narrative Review of Cardiovascular and Oncological Implications

Menatalla Mohamed Abdelmonem Mohamed[1,*], Maha Mostafa Mohamed Ibrahim Taha[1], Mohnd Moustafa Mohamed Roushdy Ibrahim[1]

1-October 6 University, 6th of October City, Giza, Egypt

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ABSTRACT

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) has surpassed viral hepatitis as the primary driver of chronic liver disease globally. While traditionally viewed through the lens of hepatic progression, its clinical trajectory is increasingly defined by extrahepatic complications.
Objective: This narrative review evaluates MASLD as a manifestation of systemic metabolic failure, specifically analyzing its role in accelerating cardiovascular dysfunction and extrahepatic carcinogenesis—the two principal causes of mortality in this population.
Methods: A comprehensive literature synthesis was conducted from 2020 to December 2025, using databases including PubMed, Scopus, and the Egyptian Knowledge Bank (EKB) to identify high-impact studies and international guidelines.
Results: The pathophysiology involves a metabolic cascade whereby hepatic lipid accumulation and insulin resistance trigger systemic inflammatory signaling. Disrupted lipid handling and genetic determinants promote pro-atherogenic and pro-oncogenic environments. The review advocates a transition to risk-stratified approaches using noninvasive biomarkers, such as the FIB-4 index.
Conclusion: Addressing the bidirectional relationship between hepatic steatosis and systemic comorbidities requires a multidisciplinary therapeutic strategy. This framework provides a basis for early intervention to reduce the burden of cardiovascular events and malignancy among patients with MASLD.

1. Introduction

The specific diagnostic criteria and alcohol consumption thresholds for MASLD, alongside other subcategories of steatotic liver disease, are summarized in **(Table 1)** [1, 2].

In 2023, a global Delphi consensus reclassified non-alcoholic fatty liver disease (NAFLD) as metabolic dysfunction-associated steatotic liver disease (MASLD) to better reflect the underlying pathophysiological drivers of the condition. The transition from NAFLD to MASLD reflects a clinical effort to remove the stigma associated with the former terminology and to more accurately emphasize the central role of metabolic dysfunction in disease progression.

Globally, MASLD affects more than one-third of the adult population [2]. The diagnostic framework requires the identification of hepatic steatosis in combination with at least one of five cardiometabolic risk factors (CMRF): overweight/obesity, hyperglycemia, hypertension, hypertriglyceridemia, or low HDL-cholesterol. This requirement distinguishes MASLD from other forms of steatotic liver disease, emphasizing the systemic nature of the condition [2, 3].

Although hepatic steatosis itself is often clinically silent, MASLD is associated with an increased risk of cirrhosis, hepatocellular carcinoma (HCC), and liver-related mortality. Paradoxically, however, cardiovascular disease remains the leading cause of death in affected individuals. This mortality is driven primarily by the systemic metabolic milieu rather than by hepatic steatosis in isolation [2]. This review aims to outline the current understanding of MASLD pathophysiology, evaluate its relationship with cardiometabolic risk, examine the mechanisms linking MASLD to cardiovascular and oncological outcomes, and summarize contemporary diagnostic and therapeutic strategies [1, 2].

1.1. Nomenclature and Definitions

To ensure clinical clarity, this review adopts the 2023 Multi-Society Consensus nomenclature: MASLD (Metabolic Dysfunction-Associated Steatotic Liver Disease): Defined by the presence of hepatic steatosis plus at least one of five cardiometabolic risk factors (CMRF), with no other discernible cause and minimal alcohol consumption (≤ 20g/day for females; ≤ 30g/day for males) [1, 3].

MetALD (Metabolic Dysfunction and Alcohol-Associated Liver Disease): Describes individuals who meet MASLD criteria but consume greater amounts of alcohol (20-50g/day for females; 30-60 g/day for males) [3, 4].

* Corresponding author: Menatalla Mohamed Abdelmonem Mohamed Faculty of Medicine, October 6 University, 6th of October City, Giza, Egypt. Email: mennahathout1@gmail.com

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Table 1: Evolution of SLD Nomenclature and Diagnostic Criteria

Category	Definition	Alcohol Consumption Thresholds	Cardiometabolic Criteria
MASLD	Hepatic steatosis + ≥ 1 CMRF [1, 3]	≤ 20g/day (F); ≤ 30g/day (M) [3]	Required [3]
MetALD	Hepatic steatosis + ≥ 1 CMRF + Alcohol [1, 3]	20 – 50g/day (F); 30 – 60g/day (M) [3]	Required [3]
ALD	Steatosis driven by alcohol [1]	Not Required [3]	Not Required [3]
Cryptogenic SLD	Steatosis with no clear etiology [3]	Minimal to none [3]	None [3]

Acronyms: ALD, alcohol-associated liver disease; CMRF, cardiometabolic risk factors; F, female; M, male; MASLD, metabolic dysfunction–associated steatotic liver disease; MetALD, metabolic dysfunction–associated with increased alcohol intake; SLD, steatotic liver disease.
Notes: Alcohol consumption thresholds are defined as daily intake [1, 3]. Cardiometabolic criteria require the presence of at least one of five specific risk factors (e.g., BMI, fasting glucose, blood pressure, or lipid levels) [3].
Source: Adapted from Adinolfi et al., 2026. [1], based on the 2023 multi-society consensus [3].

MASH (Metabolic Dysfunction-Associated Steatohepatitis): The inflammatory stage of MASLD, characterized by hepatocyte ballooning and inflammation, with or without fibrosis [3, 5].

1.2. Literature Search Strategy

To ensure a comprehensive synthesis of the current evidence regarding MASLD and its multisystemic implications, a literature search was conducted in PubMed, Scopus, Elsevier (ScienceDirect), and the Egyptian Knowledge Bank (EKB). A primary search was conducted for 2020 – 2025, with the inclusion of landmark historical studies where appropriate for the pathophysiological context. Keywords and MeSH terms included "MASLD," "steatotic liver disease," "cardiovascular risk," and "extrahepatic malignancy." Selection was prioritized for high-impact longitudinal studies, meta-analyses, and international society guidelines to ensure the clinical relevance and quality of the narrative synthesis.

2. Epidemiology

2.1. Global Prevalence and Trends

MASLD is currently the most prevalent chronic liver disease worldwide. Recent epidemiological data indicate that global adult prevalence has reached approximately 38% [6], a significant increase from the 25% reported in the previous decade. This trend parallels the rising global incidence of obesity and type 2 diabetes mellitus (T2DM). Longitudinal projections suggest that if current metabolic trends persist, global prevalence may exceed 50% by 2040 [7, 8].

2.2. Regional Heterogeneity

The distribution of MASLD exhibits significant geographic variation, influenced by a combination of genetic predisposition, dietary patterns, and socioeconomic factors: North America: Prevalence is estimated to be between 35% and 40%, attributed to high caloric intake and sedentary lifestyles [6–8].

2.2.1. Asia

Historically lower, prevalence is increasing rapidly, currently estimated at 30 – 34%. This region is notable for the "Lean MASLD" phenotype, occurring in individuals with a normal Body Mass Index (BMI) [7, 9].

2.2.2. Europe

Estimates range from 25% to 30%. While the overall prevalence is lower than in North America, the aging demographic contributes to a higher burden of advanced hepatic fibrosis [6, 8].

2.2.3. MENA and Egypt:

The Middle East and North Africa (MENA) region reports the highest global prevalence, ranging from 36% to 42%. In Egypt, prevalence exceeds 40%, correlating with high regional rates of insulin resistance [6].

2.3. Prevalence in High-Risk Cohorts

The burden of MASLD is disproportionately concentrated within populations characterized by pre-existing metabolic dysfunction: Type 2 Diabetes: 65 – 70% of patients with T2DM are affected by MASLD, with a heightened risk for progression to advanced fibrosis [7].

2.3.1. Severe Obesity

In individuals with a BMI > 35 kg/m^2, prevalence exceeds 90% [7].

2.3.2. Type 1 Diabetes

Recent evidence suggests that MASLD affects approximately 22% of adults with Type 1 Diabetes, highlighting the impact of exogenous insulin-related weight gain and metabolic health in this cohort [4].

3. Pathophysiology

MASLD pathophysiology is characterized by the disruption of hepatic lipid homeostasis, where imbalances in lipid uptake, de novo lipogenesis, β-oxidation, and export lead to hepatocellular triglyceride accumulation. Lipotoxic intermediates induce oxidative stress, endoplasmic reticulum stress, and mitochondrial dysfunction, activating proinflammatory and profibrotic signaling pathways. Persistent hepatocyte injury promotes hepatic stellate cell activation and extracellular matrix deposition, driving fibrosis and progressive liver dysfunction. The disease reflects systemic metabolic dysregulation, with contributions from adipose tissue, gut-derived factors, and insulin resistance amplifying hepatic pathology **(Figure 1)** [10].

3.1. Hepatic Lipid Metabolism

The disease initiates when at least one cardiometabolic criterion – such as obesity or T2DM – is present, shifting the liver into a state of chronic lipid surplus [3]. Hepatic steatosis develops when the delivery of free fatty acids (FFAs) and internal lipid synthesis surpasses the liver's capacity for oxidation or export via very-low-density lipoproteins (VLDL) [11, 12].

The FFAs supplying this overload originate from adipose-tissue lipolysis (≈ 59%), followed by hepatic DNL (≈ 26%), and dietary intake (≈ 15%) [13, 14]. In the setting of insulin resistance, the liver paradoxically increases DNL while failing to suppress the flux of fatty acids mobilized from peripheral fat stores [14, 15]. This

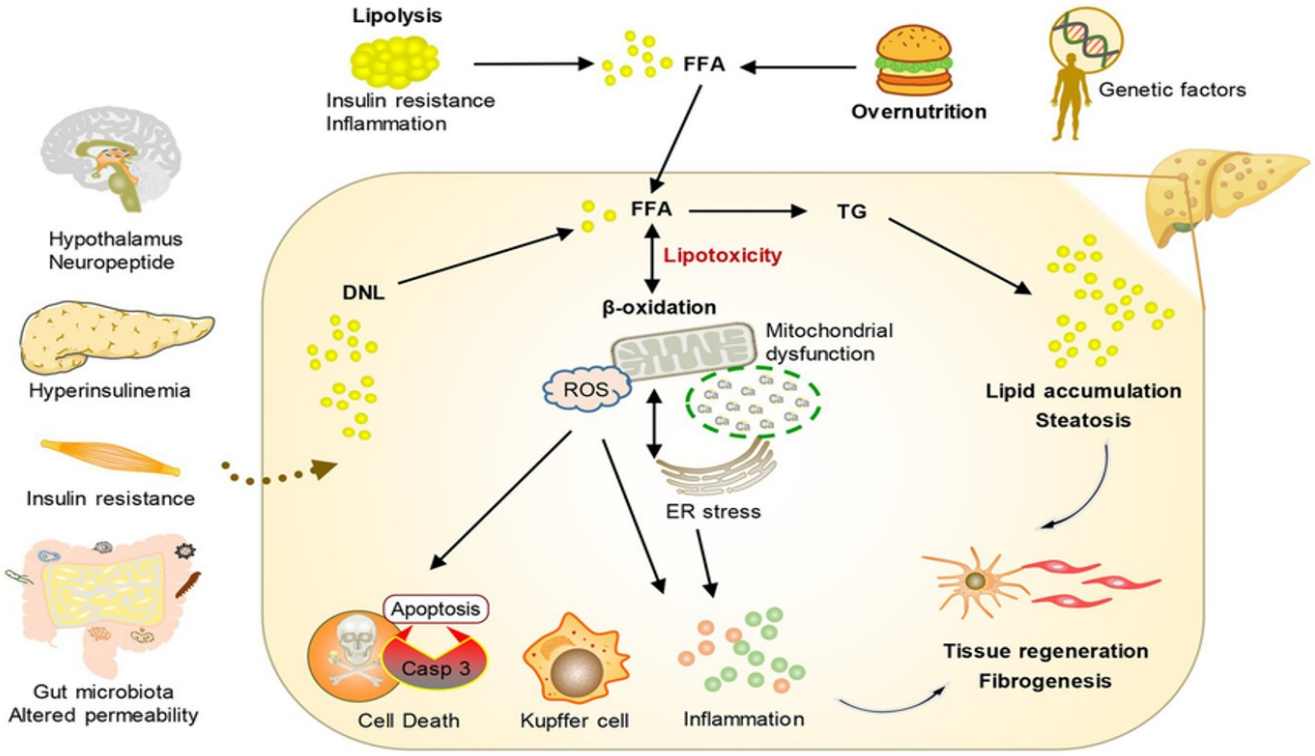

Figure 1: Conceptual diagram of the pathogenesis of MASLD. This diagram illustrates the complex interplay between overnutrition, insulin resistance, and mitochondrial dysfunction leading to hepatic fibrogenesis. Key drivers include the gut-liver axis (altered permeability), hypothalamic neuropeptide signaling, and lipotoxicity driven by free fatty acid (FFA) accumulation.

Acronyms: Casp 3, caspase-3; DNL, de novo lipogenesis; ER, endoplasmic reticulum; FFA, free fatty acids; ROS, reactive oxygen species; TG, triglycerides.

Mechanistic Note: Programmed cell death (apoptosis) and Kupffer cell activation serve as critical mediators of the transition from simple steatosis to inflammation and fibrogenesis.

Source: Adapted from Rao et al., 2023 [10].

imbalance generates toxic lipid intermediates that trigger oxidative stress and organelle dysfunction, marking the transition from simple storage to active hepatic injury [16, 17].

3.2. Insulin Resistance

This lipid buildup directly drives insulin resistance through a specific biochemical cycle [18]. As lipids like diacylglycerol (DAG) accumulate in hepatocytes, they activate PKCε, which impairs insulin receptor signaling and prevents the liver from regulating glucose production effectively [19–21].

Simultaneously, inflammatory signaling pathways – activated by excess saturated fatty acids – further disrupt insulin signaling through the phosphorylation of insulin receptor substrate-1 (IRS-1) [22, 23]. This creates a self-sustaining loop: insulin resistance promotes further lipid accumulation, which in turn exacerbates systemic inflammatory signaling and progressive metabolic failure [22, 24].

3.3. Inflammation and Cellular Injury

Metabolic stress triggers the innate immune system, characterizing the advanced stages of disease progression. Lipotoxicity-induced stress causes mitochondrial dysfunction and the leakage of reactive oxygen species (ROS), resulting in cellular damage and the release of damage-associated molecular patterns (DAMPs) [5, 25].

These DAMPs function as a critical bridge in the "multiple hit" cascade **(Figure 2)**, linking metabolic lipotoxicity to innate immune activation [5, 25, 26]. They activate Kupffer cells (resident macrophages) and trigger the NLRP3 inflammasome [5, 27]. This immune response produces pro-inflammatory cytokines (IL-1β and IL-18) and promotes distinct modes of cell death **(Table 2)** [27, 28]. This chronic cycle of hepatocyte death and inflammatory activation eventually triggers hepatic stellate cells to deposit collagen, driving the progression from simple steatosis to irreversible fibrosis [27].

4. Risk Factors and Associated Conditions

MASLD arises from a complex synergy of metabolic, genetic, and lifestyle factors. Insulin resistance (IR) serves as the central engine, stimulating hepatic de novo lipogenesis and increasing the flux of free fatty acids from dysfunctional adipose tissue [13, 14]. Visceral adiposity exacerbates this state by releasing pro-inflammatory cytokines that impair systemic lipid buffering [12]. Collectively, T2DM, dyslipidemia, and hypertension cluster to amplify the risk of advanced hepatic fibrosis and adverse cardiovascular outcomes [5, 6].

4.1. Major Risk Factors

4.1.1. Type 2 Diabetes (T2DM)

T2DM independently doubles the risk of hepatocellular carcinoma and liver-related mortality, significantly accelerating the transition from simple steatosis to advanced fibrosis [30–32].

4.1.2. Obesity and Dyslipidemia

Excess adiposity and atherogenic dyslipidemia increase the hepatic fatty acid load, triggering chronic oxidative stress [5, 6, 33].

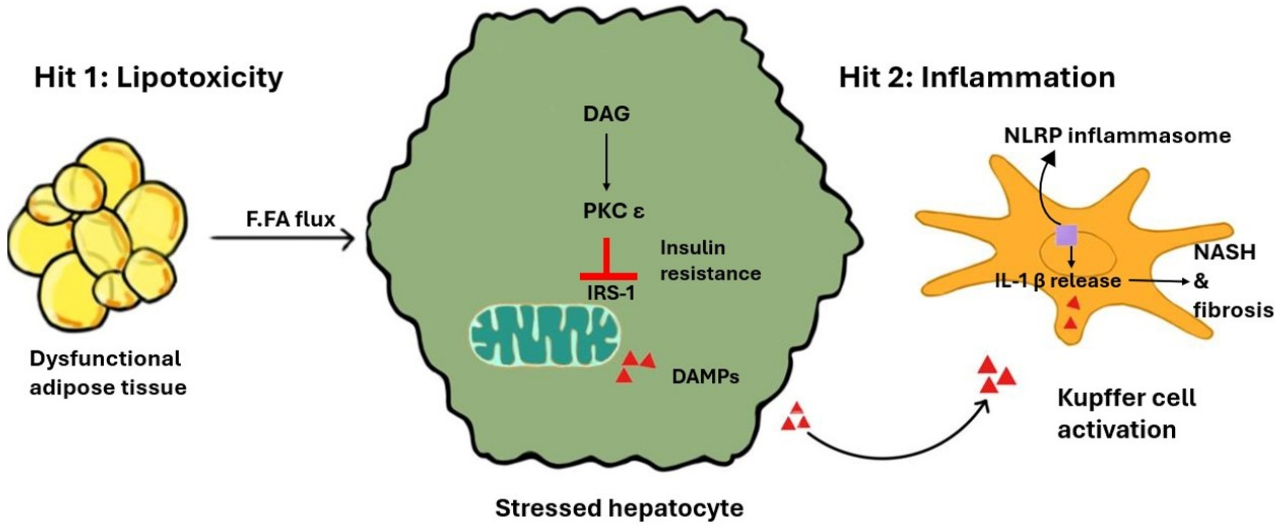

Figure 2: Multiple-Hit Pathogenesis. This illustration highlights how metabolic lipotoxicity (Hit 1) leads to innate immune activation, hepatocyte stress, and subsequent inflammation (Hit 2).
Acronyms: DAG, diacylglycerol; DAMPs, damage-associated molecular patterns; IRS-1, insulin receptor substrate 1; NLRP3, NOD-, LRR-, and pyrin domain-containing protein 3; PKCε, protein kinase C epsilon.
Nomenclature: NASH is used here as the histological equivalent of MASH.
Source: Illustration by Takwa Mohamed Hathout. Data adapted from Rinella et al. (2023) [3].

Table 2: Modes of Hepatocyte Death in MASLD

Mode of Death	Primary Mechanism	Role in MASLD Progression	Key References
Apoptosis	Caspase-dependent programmed cell death.	Initial response to lipotoxic stress; markers (e.g., CK-18) correlate with disease activity.	[5, 28]
Pyroptosis	NLRP3 inflammasome-mediated; involves Gasdermin D.	Highly inflammatory; promotes rapid cytokine release (IL-1β) and stellate cell activation.	[27]
Ferroptosis	Iron-dependent lipid peroxidation.	Driven by ROS and impaired antioxidant capacity; critical in the transition to MASH.	[28]
Necroptosis	RIPK1/RIPK3-mediated regulated necrosis.	Promotes massive DAMP release and severe sterile inflammation.	[5]

Hepatocyte death is the primary driver of progression from simple steatosis to MASH (Metabolic Dysfunction-Associated Steatohepatitis), the inflammatory stage of metabolic liver disease [24, 29]. Each pathway contributes differently to liver injury: Apoptosis is a programmed cell death mediated by caspases; Pyroptosis is a highly inflammatory response involving the NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome [25, 27]; Ferroptosis is an iron-dependent form of death caused by ROS (Reactive Oxygen Species) [26, 28]; and Necroptosis is a regulated necrosis involving RIPK1/RIPK3 that releases DAMPs (Damage-Associated Molecular Patterns) to trigger sterile inflammation [5].
Acronyms: CK-18, cytokeratin-18; MASH, metabolic dysfunction–associated steatohepatitis; RIPK, receptor-interacting protein kinase; ROS, reactive oxygen species.
Notes: This table summarizes the biochemical markers and triggers for various cell death pathways identified in steatotic hepatocytes.
Source: Synthesized from current literature (2020 – 2025).

4.1.3. Genetic Predisposition
Variants such as PNPLA3 (impaired lipid droplet hydrolysis) and TM6SF2 (disrupted VLDL export) significantly influence disease susceptibility and the velocity of fibrosis progression [13, 27, 34].

4.2. Associated Conditions
4.2.1. Dietary Factors
High-calorie diets rich in fructose and saturated fats are potent stimulators of fat synthesis. Fructose is particularly damaging as it bypasses normal metabolic checks to drive triglyceride production [13, 14, 16].

4.2.2. Gut-Liver Axis (SIBO)
Small-intestinal bacterial overgrowth promotes increased intestinal permeability. This facilitates the translocation of lipopolysaccharides (LPS) into the portal circulation, activating Toll-like receptors and exacerbating hepatocellular injury [15, 25].

4.2.3. Obstructive Sleep Apnea
Chronic intermittent hypoxia associated with OSA induces systemic oxidative stress and sympathetic overactivity, which intensify hepatic inflammatory signaling [13, 19, 25].

4.2.4. Endocrine and Hormonal Factors:
Hypothyroidism: Low thyroid hormones decrease the liver's ability to oxidize fat and export VLDL [6, 33].

Hyperuricemia: High uric acid promotes insulin resistance and stresses liver mitochondria [22, 24].

Polycystic Ovary Syndrome (PCOS): Hyperinsulinemia in PCOS promotes direct hepatic fat production [13, 19].

4.3. The "Lean MASLD" Phenotype

"Lean MASLD" occurs in individuals with a normal Body Mass Index (BMI 18.5 – 24.9 kg/m^2) who exhibit at least one cardiometabolic risk factor [2, 4].

Adipose Tissue Dysfunction: Pathogenesis is frequently driven by the limited expansion capacity of peripheral adipose tissue. When subcutaneous storage thresholds are exceeded, lipids are diverted to ectopic sites, resulting in significant hepatic accumulation [12, 13].

4.3.1. Genetic Influence

This phenotype is strongly associated with the PNPLA3 variant, explaining the presence of significant hepatic fat despite lower systemic adiposity [4, 13].

4.4. Metabolic Drivers of Malignancy

The pro-inflammatory and hyperinsulinemic state of MASLD creates a systemic environment conducive to carcinogenesis.

4.5. Established Associations:

4.5.1. Hepatocellular Carcinoma (HCC)

MASLD is a primary driver of primary liver malignancy. Distinctively, HCC in the context of MASLD frequently occurs in the absence of established cirrhosis, suggesting that lipotoxicity-induced DNA damage and chronic oxidative stress can initiate malignant transformation independently of advanced fibrosis [35–38].

4.5.2. Colorectal Cancer (CRC)

MASLD is associated with a 60% increase in CRC risk [39]. Pathophysiology likely involves the disruption of the gut-liver axis and the systemic elevation of insulin-like growth factor 1 (IGF-1), which promotes colonic epithelial proliferation and inhibits apoptosis [40].

4.6. Emerging Clinical Associations

4.6.1. Breast and Gynecological Malignancies:

MASLD is linked to a 20 – 40% higher incidence of breast cancer, particularly in postmenopausal women. The proposed mechanism involves the aromatization of androgens in adipose tissue and the resulting estrogenic stimulation of breast and uterine tissues [39, 41].

4.6.2. Thyroid and Pulmonary Malignancies

Recent data indicate an association between MASLD and more aggressive phenotypes of thyroid cancer. Furthermore, systemic inflammatory cytokines – specifically IL-6 and TNF-α – may synergize with environmental factors to increase lung cancer risk, though obesity remains a significant confounding variable in these cohorts [41].

5. Extrahepatic Manifestations

MASLD is a systemic multisystem disorder; its presence serves as a sentinel marker for clinical deterioration in other organ systems. While metabolic factors drive the initial liver injury, the resulting chronic systemic inflammation and shared pro-fibrotic pathways lead to significant complications outside the liver [34, 35, 42].

5.1. Cardiovascular Manifestations

Cardiovascular disease (CVD) is the leading cause of death in MASLD patients, often exceeding liver-related mortality. The liver's inflammatory state directly contributes to cardiac structural and electrical remodeling:

5.1.1. Heart Failure

MASLD independently raises the risk of incident heart failure, particularly Heart Failure with preserved Ejection Fraction (HFpEF), by approximately 50% [42, 43].

5.1.2. Structural Remodeling:

Patients frequently exhibit subclinical changes, including left ventricular hypertrophy and impaired diastolic filling, even in the early stages of liver fat accumulation [42].

5.1.3. Arrhythmias:

There is a robust association with Atrial Fibrillation, likely driven by pro-inflammatory cytokines originating from both the liver and epicardial adipose tissue [42–44].

5.2. Extrahepatic Malignancies

The pro-oncogenic environment of MASLD – characterized by hyperinsulinemia and chronic low-grade inflammation – extends beyond the liver to several extrahepatic sites [35, 36, 45]:

5.2.1. Colorectal Cancer (CRC):

MASLD is associated with a 60% higher risk of CRC and a significant increase in colorectal adenomas. This association is strongest in patients with advanced fibrosis, necessitating vigilant screening [39, 40, 46].

5.2.2. Gastrointestinal and Other Cancers:

Increased risks are noted for esophageal and gastric cancers [41]. Emerging evidence also suggests a higher incidence of breast and thyroid malignancies, often presenting with more aggressive clinical features [35, 41].

5.3. Renal and Endocrine Manifestations

The crosstalk between the liver and other metabolic organs creates a cycle of systemic decline:

5.3.1. Chronic Kidney Disease (CKD):

MASLD is an independent risk factor for CKD. Pro-inflammatory and pro-fibrotic signals (such as TGF-β) released by the liver promote glomerular damage and decline renal function [34, 43].

5.3.2. Metabolic Feedback Loops:

While insulin resistance drives MASLD, the presence of hepatic steatosis conversely makes glycemic control more difficult in patients with T2DM, increasing the likelihood of diabetic microvascular complications [29, 47].

6. Diagnosis and Risk Stratification

Diagnosis requires the identification of hepatic steatosis via imaging or histology, the presence of ≥ 1 cardiometabolic risk factor (CMRF), and the systematic exclusion of competing etiologies [2, 3].

6.1. Laboratory Assessment and Differential Diagnosis

Transaminases (ALT/AST) are poor exclusionary tests; a normal ALT does not exclude advanced fibrosis. Clinical suspicion should remain high in patients with T2DM or obesity regardless of enzyme levels [4, 33].

Table 3: Performance, thresholds, and limitations of non-invasive modalities for hepatic steatosis and fibrosis assessment

Modality	Performance and Thresholds	Limitations
Ultrasonography	High specificity (98%) for moderate/severe steatosis.	Sensitivity drops if fat content < 20% or BMI > 40 kg/m^2 [6].
FIB-4 Index	• < 1.3 (Low Risk): NPV > 90% for F3/F4 [4, 33]. • 1.3–2.67: Indeterminate [1, 3]. • > 2.67 (High Risk): Refer to hepatology [1, 4].	Accuracy decreases in patients < 35 or > 65 years old [4].
• VCTE (FibroScan)	• < 8 kPa (Low Risk): Rules out advanced fibrosis [33]. • 8-12 kPa: Indeterminate [3, 48]. • > 12–15 kPa (High Risk): Highly suggestive of F3/F4 [4, 33].	Reduced reliability in severe obesity (BMI > 35) without XL probes [33].
• MRI-PDFF	Gold standard for fat quantification (> 5% threshold) [1, 48].	High cost; limited availability for routine monitoring [6].

The diagnostic utility of these modalities depends on their ability to accurately stage fibrosis, as increasing stiffness values correlate with higher risks of liver-related complications. FIB-4 (Fibrosis-4 Index) serves as a high-sensitivity triage tool to rule out advanced disease in primary care [4, 33], whereas VCTE (Vibration-Controlled Transient Elastography) and MRI-PDFF (Proton Density Fat Fraction) provide quantitative assessments of liver stiffness and hepatic fat content, respectively [1, 33, 48]. While NITs (Non-Invasive Tests) offer a safe alternative to biopsy, their accuracy is influenced by the NPV (Negative Predictive Value), which remains the primary metric for excluding advanced fibrosis in at-risk populations [3, 48].
Acronyms: FIB-4, Fibrosis-4 Index; MRI-PDFF, Magnetic Resonance Imaging Proton Density Fat Fraction; NPV, Negative Predictive Value; VCTE, Vibration-Controlled Transient Elastography; LSM, Liver Stiffness Measurement; CAP, Controlled Attenuation Parameter; ELF, Enhanced Liver Fibrosis.
Notes: Performance ranges are based on evidence-based thresholds; operator dependence and patient obesity are noted as primary limitations [33].
Source: Compiled from AASLD and EASL clinical practice guidelines.

6.1.1. Transaminase Thresholds:
While lab ranges vary, an ALT > 30 U/L is increasingly recognized as the threshold for further evaluation in adults [4].

6.1.2. Differential Diagnosis:
To confirm MASLD, the following must be excluded:

- Metabolic Dysfunction-Associated and Increased Alcohol Intake (MetALD): A distinct category for patients meeting MASLD criteria but with higher alcohol intake (20-50g/day for females; 30-60g/day for males) [3].
- Alcohol-associated Liver Disease (ALD): Defined by chronic intake exceeding 50g/day in females or 60g/day in males. Clinical suspicion is supported by AUDIT/CAGE scores, and an AST:ALT ratio > 2; suggests alcohol use or advanced cirrhosis [3, 33].
- Viral Hepatitis: HBsAg and anti-HCV screening [6].
- Hereditary Hemochromatosis: Transferrin saturation > 45% and elevated ferritin [33].
- Drug-Induced Steatosis: Review use of amiodarone, methotrexate, or chronic corticosteroid use [13, 16].
- Rare Etiologies: Wilson disease or Autoimmune Hepatitis should be considered in younger cohorts or those with atypical biochemical profiles (e.g., low-titer autoantibodies and high IgG) [33].

6.2. Imaging and Non-Invasive Tests
The diagnostic goal is to identify Advanced Fibrosis (F ≥ 3), as this is the primary predictor of liver-related mortality.

While imaging is central to diagnosis, clinicians must recognize its technical boundaries. Conventional ultrasound has a sensitivity of only 60 – 90% for detecting steatosis, often failing when the fat fraction is below 20% [6, 24]. Furthermore, the accuracy of VCTE is highly operator-dependent and significantly limited by the 'skin-to-capsule' distance in patients with morbid obesity, which can lead to falsely elevated LSM readings [33]. Despite standardized cutoffs, diagnostic uncertainty persists within 'indeterminate' ranges (e.g., FIB-4 1.3 – 2.67 or VCTE 8 – 12 kPa), where guidelines vary on whether to prioritize immediate secondary testing or longitudinal monitoring [1, 3, 48] **(Table 3)**.

6.3. Clinical Referral and Management Pathway
Following the AASLD/EASL 2023 consensus, the clinical pathway follows a tiered approach **(Figure 3)**:

6.3.1. Tier 1 (Low Risk)
Calculate FIB-4 for all at-risk patients , including those with T2DM or obesity. If FIB-4 < 1.3, advanced fibrosis is ruled out with high negative predictive value; these patients should repeat non-invasive tests in 2 – 3 years and focus on cardiovascular disease (CVD) risk reduction. [3, 4, 33].

6.3.2. Tier 2 (Indeterminate Risk)
For FIB-4 1.3 – 2.67, perform a secondary non-invasive test such as VCTE or the Enhanced Liver Fibrosis (ELF) test. If results remain indeterminate, patients should be reassessed annually or referred based on clinical suspicion [3, 4].

6.3.3. Tier 3 (Specialist Care)
Patients with FIB-4 > 2.67 or LSM ≥ 12 kPa are considered high-risk and require hepatology referral. Confirmed advanced fibrosis (F3/F4) necessitates the initiation of MASH management, biannual HCC screening, and formal variceal risk assessment [3, 4, 33].

6.4. The Role of Liver Biopsy
Biopsy is no longer first-line but remains indicated when:

- NITs are indeterminate or discordant with clinical presentation.
- Alternative or co-existing liver diseases (e.g., Autoimmune Hepatitis) are suspected.
- Participation in clinical trials for MASH-targeted therapies [13].

6.5. Management of Advanced Fibrosis (F3) and Cirrhosis (F4)
Patients identified with advanced fibrosis (F3) or with compensated advanced chronic liver disease (cACLD) (F4) require a structured

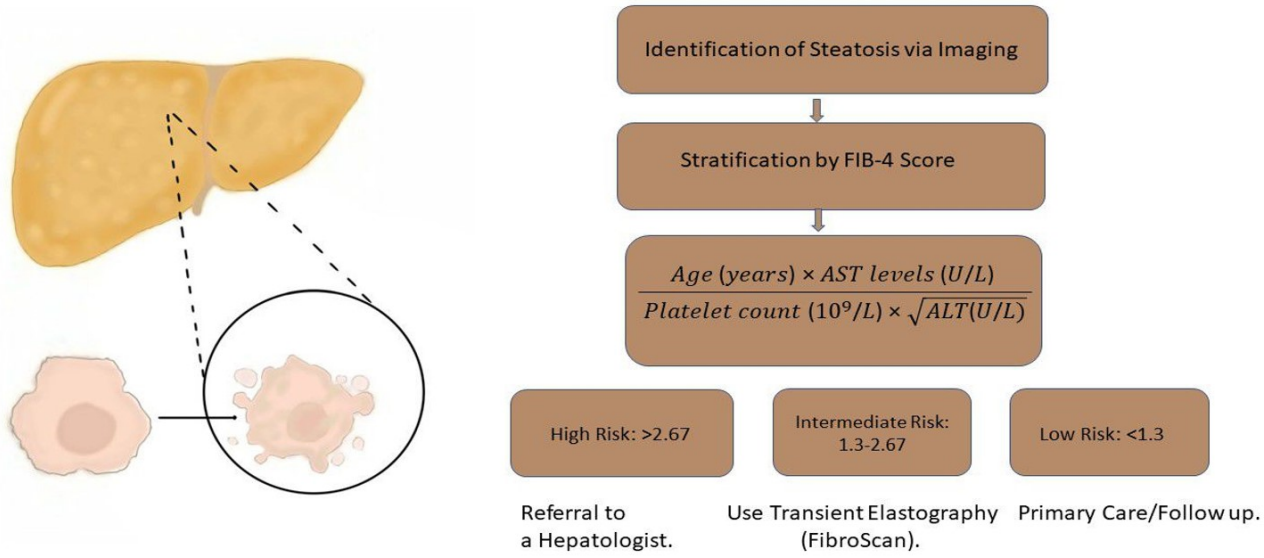

Figure 3: FIB-4 Risk Stratification Flowchart. A tiered clinical approach for primary care triage. Patients with a FIB-4 score < 1.3 (or < 2.0 for those aged > 65) are considered low risk [3, 33]. Those in the Indeterminate Risk category (FIB-4 1.3 – 2.67) require secondary testing [4]. Finally, patients with a score > 2.67 – or high-risk patients – require specialized hepatology referral [3].
Acronyms: ALT: alanine aminotransferase; AST: aspartate aminotransferase.
Source: Illustration by Gana Mohamed and Takwa Hathout. Adapted from AASLD/EASL 2023 guidelines.

care bundle to mitigate the risks of decompensation and mortality. This multifaceted approach includes:

6.5.1. HCC Surveillance
Mandatory biannual abdominal ultrasound (± alpha-fetoprotein) for all patients with cirrhosis (F4) and considered for those with F3 based on individual risk [30, 35, 38].

6.5.2. Portal Hypertension
According to the Baveno VII criteria, screening endoscopy for esophageal varices can be safely avoided in patients with a liver stiffness measurement < 20 kPa AND a platelet count > 150,000/L. Conversely, those not meeting these criteria require endoscopic screening [3, 4, 48].

6.5.3. Transplant Referral
Explicit referral for liver transplantation assessment is triggered by a MELD-Na score ≥ 15, the first occurrence of hepatic decompensation (ascites, encephalopathy, or jaundice), or HCC within Milan criteria [4, 48] Decompensation Monitoring: Regular clinical surveillance for complications such as ascites, hepatic encephalopathy, and variceal hemorrhage is essential for patients cACLD [3, 48].

6.5.4. Vaccination
Routine immunization against hepatitis A (HAV), hepatitis B (HBV), and pneumococcus, as well as annual influenza and COVID-19 boosters, is necessary to prevent acute-on-chronic liver failure [1, 4, 48].

6.5.5. Nutritional Support
Targeted intervention for sarcopenia involves a protein-rich diet (1.2 – 1.5 g/kg/day) and Vitamin D optimization to preserve bone mineral density [48].

6.5.6. Metabolic & Bone Health
Regular screening for osteoporosis/osteopenia and Vitamin D deficiency [1, 48].

6.6. Management and Treatment
The primary objectives in MASLD management are to achieve histological resolution of MASH and to cease or reverse fibrosis, thereby modifying the risk of cirrhosis, hepatocellular carcinoma, and liver-related mortality [1, 4, 24, 48]. Concurrent management of the cardiometabolic cluster – obesity, T2DM, dyslipidemia, and hypertension – is mandatory to reduce extrahepatic risks, including chronic kidney disease and heart failure [2, 29, 47].

6.7. Lifestyle and Behavioral Interventions
Lifestyle modification remains the non-pharmacological basis of therapy. Weight loss exhibits a dose-response relationship with histological improvement:

- >5% Weight Loss: Sufficient to reduce hepatic steatosis.
- 7–10% Weight Loss: Associated with significant MASH resolution (64% vs. 10% in those losing <5%) and improvement in inflammation [48].
- >10% Weight Loss: Offers the highest rates of benefit, with 90% MASH resolution and 45% fibrosis regression at 52 weeks [48].

6.8. Dietary and Physical Activity Protocols
6.8.1. Dietary Patterns
Beyond general weight loss, the Mediterranean Diet is uniquely effective due to its high concentration of monounsaturated fatty acids and antioxidants. These components directly influence hepatic de novo lipogenesis and systemic inflammation, leading to superior metabolic outcomes compared to standard low-fat diets [4, 48, 49].

Table 4: Comparing Pharmacotherapy for MASH

Agent	Class / Primary Indication	Key Histological Outcome
Resmetirom	THR-β Agonist; MASH with F2 – F3 fibrosis [1, 9].	25% Fibrosis improvement; 30% MASH resolution [9, 48].
Semaglutide	GLP-1 RA; Obesity and T2DM [48, 50].	
Tirzepatide	GIP/GLP-1 RA; Obesity and T2DM [9, 50].	62.8% MASH resolution; signal for fibrosis improvement [50].
Pioglitazone	PPAR-γ Agonist; T2DM (off-label for MASH) [4, 48].	Improved steatohepatitis; risk of weight gain [4, 48].

Therapeutic selection is increasingly guided by the patient's clinical phenotype. Resmetirom is prioritized for patients requiring direct fibrosis regression in non-cirrhotic (F2 – F3) stages, based on the MAESTRO-NASH trial outcomes [9]. Incretin mimetics (GLP-1 and dual GIP/GLP-1 RAs) are favored for those with high cardiometabolic risk, obesity, or Type 2 Diabetes Mellitus [48, 50]. Outcome data represent results from primary clinical endpoints: MASH resolution (defined as the disappearance of ballooning and inflammation) and/or fibrosis improvement [9, 50]. Non-invasive monitoring via MRI-PDFF and LSM provides surrogate assessments of treatment response [33, 42].
Acronyms: GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide; MASH, metabolic dysfunction – associated steatohepatitis; RAs, receptor agonists; THR-β, thyroid hormone receptor-beta.
Source: Adapted from Rinella et al. (2023) [3], Eddowes et al. (2019) [33], and primary clinical trial data [9, 50].

6.8.2. Exercise

Guidelines recommend 150 minutes of moderate-intensity aerobic activity or 75 – 150 minutes of vigorous activity weekly. Exercise improves hepatic insulin sensitivity and reduces liver fat even in the absence of significant weight change [1, 4, 48].

6.9. Pharmacotherapy: The 2024 – 2025 Shift

Until recently, pharmacotherapy was limited to off-label use of vitamin E or pioglitazone. The landscape has been transformed by the approval of targeted agents and high-potency incretin therapies **(Table 4)**:

6.9.1. Resmetirom

A selective thyroid hormone receptor-β (THR-β) agonist approved for non-cirrhotic MASH. It achieved MASH resolution in ˜30% and fibrosis improvement in 25% of trial participants. [9].

6.9.2. Incretin Mimetics

Semaglutide and Tirzepatide have demonstrated MASH resolution rates exceeding 60%. While primary indications are obesity and T2DM, they significantly improve the metabolic environment and reduce liver stiffness [42, 50].

It is critical to distinguish between the evidence levels of current therapeutics [4]. Resmetirom and Tirzepatide have demonstrated efficacy based on histological endpoints (biopsy-proven MASH resolution and fibrosis reversal) [9, 50], which remain the gold standard for regulatory approval. Conversely, many early-stage incretin studies rely on surrogate outcomes, such as significant reductions in MRI-PDFF (Magnetic Resonance Imaging Proton Density Fat Fraction) or LSM, which correlate with clinical improvement but do not yet confirm tissue-level fibrosis regression [33, 42].

6.10. Bariatric Surgery

Bariatric procedures (Roux-en-Y gastric bypass or sleeve gastrectomy) are highly effective for patients with a BMI > kg/m^2 and refractory MASH [32, 48].

6.10.1. Long-term Outcomes

At 5 years post-surgery, up to 84% of patients achieve MASH resolution and 70% show fibrosis improvement [48].

6.10.2. Hard Outcomes

Large observational studies confirm that bariatric surgery reduces 10-year major liver-related events (2.3% vs. 8.5%) and cardiovascular events (8.5% vs. 15.7%) compared to non-surgical care [32, 48].

7. Complications

MASLD affects approximately 30% of the global adult population, with its prevalence having nearly doubled between 1991 and 2019 paralleling the surge in global obesity rates. MASH represents the progressive inflammatory phenotype, characterized by hepatocyte ballooning and lobular inflammation, and is the primary driver of advanced fibrosis. While cardiovascular disease (CVD) remains the leading cause of death in MASLD patients, liver-related mortality increases exponentially once patients reach advanced fibrosis stages (F3 – F4) [1, 24, 35, 48].

7.1. Type 2 Diabetes Mellitus

Type 2 Diabetes Mellitus (T2DM) is an independent risk factor for both MASH and accelerated fibrosis [51]. Because advanced fibrosis often remains asymptomatic until hepatic decompensation occurs, a risk-based assessment pathway is critical for diabetic patients:

7.1.1. Initial Screening

Utilize the FIB-4 Index as a primary case-finding tool for all diabetic patients, rather than relying on transaminases, which serve as poor rule-out tools [3, 7]

7.1.2. Confirmatory Testing

Elevated or indeterminate FIB-4 scores must be followed by Liver Stiffness Measurement via VCTE (Vibration-Controlled Transient Elastography) to improve positive predictive value [3, 4, 33].

7.2. Cardiovascular Disease (CVD)

The American Heart Association (AHA) recognizes MASLD as an independent, underappreciated risk factor for atherosclerotic cardiovascular disease. This risk is mediated by systemic metaflammation and pro-atherogenic lipid profiles [42, 43].

7.2.1. Management:

Statins are first-line, safe in MASLD, and may reduce the risk of HCC.

7.2.2. Preferred Agents

In patients with T2DM and high cardiovascular risk, SGLT2 inhibitors or GLP-1 RAs are preferred for their dual hepatic and cardioprotective benefits [42, 43]

7.3. Portal Hypertension and Variceal Risk

Clinically significant portal hypertension can manifest in compensated advanced chronic liver disease (cACLD) before symptoms appear.

7.3.1. Risk Stratification

- Liver stiffness measurement < 10 kPa: cACLD is unlikely [4, 33].
- Liver stiffness measurement > 15 kPa: Suggestive of cACLD [3, 33].
- CSPH Exclusion: Unlikely if Liver stiffness measurement < 15 kPa and platelets > 150×10^9/L [3, 48].

7.3.2. Management

Non-selective beta-blockers, particularly carvedilol, are the standard of care to reduce portal pressure and prevent the first episode of decompensation. Routine endoscopic screening for varices is not required if Liver stiffness measurement < 20 kPa and platelets > $150\times10^9/L$[3, 4, 48].

7.4. SARCOPENIA AND NUTRITIONAL OPTIMIZATION IN ADVANCED MASLD

Sarcopenia (the progressive loss of muscle mass, strength, and quality) frequently coexists with MASLD, creating a vicious cycle of physical inactivity and worsened insulin resistance. Modern clinical focus has shifted toward sarcopenic obesity (SO), which is characterized not just by low muscle volume, but by myosteatosis (fatty infiltration of the muscle). Patients with Sarcopenic obesity have a significantly higher risk of advanced fibrosis and mortality compared to those with obesity alone.

7.4.1. The Incretin Paradox

While GLP-1 and GIP/GLP-1 receptor agonists (e.g., Tirzepatide) are highly effective for weight loss, up to 25 – 40% of weight lost can be lean muscle mass. To prevent a decline in metabolic rate, these therapies must be paired with mandatory resistance training and optimized protein intake [10, 42, 50].

7.4.2. Nutritional Strategy

Overcoming "anabolic resistance" in MASLD requires a high protein intake (1.2 – 1.5 g/kg/day), distributed boluses of protein throughout the day. Adherence to a Mediterranean dietary pattern is the gold standard, as its monounsaturated fats and antioxidants specifically reduce systemic inflammation and de novo lipogenesis [16, 49].

7.4.3. Physical Intervention

Resistance exercise remains a cornerstone non-pharmacological 'liver-sparing' intervention. By improving the glucose-clearing capacity of the skeletal muscle – the body's largest metabolic organ – resistance training reduces the metabolic load on the liver independently of total weight loss [12, 19].

8. Conclusion

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a multisystem disorder driven by the convergence of hepatic lipotoxicity, insulin resistance, and systemic metaflammation [1, 48]. This cascade facilitates the progression from simple steatosis to MASH, a phenotype characterized by hepatocyte injury and fibrogenesis that may ultimately lead to cirrhosis or hepatocellular carcinoma (HCC) [4, 24]. Beyond the liver, evidence links MASLD to systemic complications, most notably cardiovascular disease and heart failure [42, 43].

The clinical approach is shifting toward risk-based screening using non-invasive tests (NITs) such as the FIB-4 index and VCTE (Vibration-Controlled Transient Elastography) [6, 12]. While these tools improve the identification of advanced fibrosis, their diagnostic accuracy can be affected by age and ethnicity, necessitating a cautious, tiered interpretation to ensure equitable care [4, 11]. Furthermore, access to these specialized diagnostic tools remains a challenge in underserved communities, which may delay diagnosis in high-risk "sentinel" populations.

Lifestyle modification, specifically a 7 – 10% reduction in body weight and adherence to a Mediterranean dietary pattern, remains the primary therapeutic recommendation [16, 49]. The recent approval of Resmetirom and the clinical promise of GLP-1 RAs represent significant progress [9, 50]. However, as these therapies move from clinical trials into general practice, ensuring broad and equitable access – regardless of socioeconomic status – is essential to preventing further health disparities in liver-related mortality [4, 9].

Ultimately, reducing the global burden of MASLD requires an integrated approach that connects hepatology with endocrine and cardiovascular care. Prioritizing early, inclusive, and evidence-based intervention is the most effective strategy to attenuate the long-term inflammatory and metabolic complications of this disease across all patient populations.

Conflicts of Interest

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Ethical approval

Not applicable. This article is a literature review and does not contain any original studies with human participants or animals performed by any of the authors.

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The authors declare that Gemini (an AI tool by Google) was used to assist with structural editing and citation management during the preparation of this manuscript. The authors reviewed and verified all scientific content and take full responsibility for the integrity and accuracy of the final work.

Authors Contribution

All authors contributed to the study conception and design. The first draft of the manuscript was written by MM, and all authors provided critical revisions to previous versions of the manuscript. All authors read and approved of the final manuscript.

Data Availability

Data sharing is not applicable to this article as no new datasets were created or analyzed during the current study.

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Review Article

The Liver-Heart Axis: A Narrative Review of Clinical Implications of the MASLD Redefinition for Internists

Hassan A. Abdou[1,*], Saied A. Omar[2]

1-Capital (Helwan) University Hospitals, Faculty of Medicine, Capital (Helwan) University, Cairo, Egypt
2-Faculty of Medicine, Ain Shams University, Cairo, Egypt

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ABSTRACT

Introduction: Metabolically-dysfunction-associated steatotic liver disease (MASLD) represents a paradigm shift emphasizing the metabolic underpinnings of hepatic steatosis and its systemic consequences. MASLD carries a substantial cardiovascular burden. This review examines the clinical implications of the MASLD redefinition for internists, with particular focus on the liver-heart axis.
Methods: We conducted a narrative review synthesizing evidence through December 2024. Literature searches were performed in PubMed, EMBASE, and Cochrane Library using terms including "MASLD," "nonalcoholic fatty liver disease," "metabolic dysfunction-associated steatohepatitis," "cardiovascular disease," and "cardiometabolic risk." Priority was given to systematic reviews, meta-analyses, and large prospective cohort studies.
Results: MASLD is associated with increased risks of coronary artery disease, myocardial infarction, heart failure with preserved ejection fraction, atrial fibrillation, and cardiovascular mortality. These associations are mediated through insulin resistance, chronic inflammation, oxidative stress, atherogenic dyslipidemia, hepatokine dysregulation, gut-derived metabolites, and genetic determinants — though substantial residual confounding by shared cardiometabolic risk factors remains. Hepatic fibrosis stage emerges as a critical amplifier of cardiovascular risk. Integrated management requires systematic case-finding, fibrosis risk stratification using validated noninvasive tools, comprehensive cardiovascular assessment, intensive lifestyle intervention, and pharmacotherapy including incretin-based therapies, sodium-glucose cotransporter-2 inhibitors, and statins.
Conclusions: Internists must adopt integrated approaches addressing both hepatic and cardiovascular manifestations of MASLD. The liver-heart axis requires recognition as an interconnected system, with cardiovascular risk management prioritized alongside hepatic care. While the MASLD nomenclature is intended to improve disease recognition and patient engagement, prospective validation of these anticipated benefits remains needed.

1. Introduction

The landscape of fatty liver disease has undergone a transformative evolution with the introduction of metabolic dysfunction-associated steatotic liver disease (MASLD) as the replacement terminology for nonalcoholic fatty liver disease (NAFLD) [1]. This nomenclature change, announced in June 2023 following a rigorous multisociety Delphi consensus process involving over 200 panelists from 56 countries, reflects more than semantic refinement. It represents a fundamental reconceptualization of fatty liver disease as an intrinsically metabolic disorder with systemic manifestations that extend far beyond the hepatic parenchyma [1, 2].

* Corresponding author: Hassan A. Abdou, Capital (Helwan) University Hospitals, Faculty of Medicine, Capital (Helwan) University, Cairo, Egypt. Email: drhassanahmedhassan-abdou@gmail.com

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The impetus for this nomenclature revision arose from multiple limitations of the NAFLD terminology. First, the term was exclusionary, defined by the absence of other liver diseases rather than by positive diagnostic criteria [2, 3]. Second, the terminology was perceived as stigmatizing, with terms such as fatty and nonalcoholic carrying negative connotations that could affect patient engagement and care-seeking behavior [3, 4]. Third, and most critically, the previous nomenclature failed to capture the metabolic dysfunction that fundamentally drives disease pathogenesis and progression [1, 5].

MASLD now affects approximately 30% of the global adult population, with prevalence rates paralleling the worldwide epidemic of obesity, type 2 diabetes mellitus, and metabolic syndrome [6, 7]. What was once considered a relatively benign hepatic condition has emerged as a dynamic, progressive disorder intimately linked to multisystem injury, with the cardiovascular system representing its most frequent and fatal extrahepatic target [8, 9]. Cardiovascular complications, including myocardial infarction, stroke, and heart failure, frequently manifest before significant hepatic events, underscoring the silent yet pervasive nature of the MASLD-cardiovascular disease (CVD) axis [8, 10].

For internists, who serve as frontline clinicians managing patients with complex cardiometabolic disorders, understanding the new

MASLD nomenclature and its implications for cardiovascular risk stratification is paramount. The liver-heart axis encompasses both a well-characterized forward pathway – wherein hepatic metabolic dysfunction promotes cardiovascular disease through shared pathophysiological mechanisms – and a clinically important but less well-studied reverse pathway – wherein primary cardiac dysfunction drives hepatic injury through hemodynamic and congestive mechanisms [11, 12]. This review addresses both directions, recognizing that internists managing patients with advanced heart failure or cardiogenic shock will frequently encounter hepatic consequences that require integrated clinical reasoning.

This comprehensive review aims to provide internists with an updated understanding of MASLD nomenclature, to explore the mechanistic underpinnings of the liver-heart axis, to examine cardiovascular outcomes associated with MASLD, to discuss diagnostic and risk-stratification approaches, and to outline integrated management strategies that address both hepatic and cardiovascular manifestations of this multisystem disease.

2. The MASLD Nomenclature: Key Changes and Definitions

2.1. The Delphi Consensus Process

The nomenclature revision process employed a modified Delphi methodology coordinated by three major liver associations: the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), and the Latin American Association for the Study of the Liver (ALEH) [1]. The process included four rounds of online surveys and two hybrid meetings, with participation from hepatologists, gastroenterologists, endocrinologists, primary care physicians, patient advocates, regulatory representatives, and pharmaceutical industry stakeholders [1, 2].

Consensus was defined a priori as a supermajority (≥67%) vote. Survey results demonstrated that 74% of participants supported a name change, 78% endorsed an overarching term to accommodate disease evolution, and 67% favored inclusion of a metabolic descriptor in the new nomenclature [1, 3]. An independent external committee of experts made the final recommendation on the acronym and diagnostic criteria.

2.2. Core Definitions and Diagnostic Criteria

2.2.1. Steatotic Liver Disease (SLD)

The umbrella term encompassing all causes of hepatic steatosis, diagnosed histologically or by imaging modalities [1, 2].

2.2.2. Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

Defined as hepatic steatosis (≥ 5% hepatic fat content) in the presence of at least one of five cardiometabolic risk factors, in the absence of other causes of hepatic steatosis [1, 13]. The five cardiometabolic risk factors include:

1. Body mass index (BMI) ≥ 25 kg/m^2 (or ≥ 23 kg/m^2 in Asian populations) or waist circumference > 94 cm in males or > 80 cm in females
2. Fasting serum glucose ≥ 100 mg/dL or 2-hour post-load glucose ≥ 140 mg/dL or hemoglobin A1c ≥ 5.7% or type 2 diabetes mellitus or treatment for type 2 diabetes
3. Blood pressure ≥ 130/85 mmHg or specific antihypertensive drug treatment
4. Plasma triglycerides ≥ 150 mg/dL or lipid-lowering treatment
5. Plasma high-density lipoprotein (HDL) cholesterol < 40 mg/dL for males and < 50 mg/dL for females or lipid-lowering treatment

2.2.3. Metabolic Dysfunction-Associated Steatohepatitis (MASH)

Replaces the term nonalcoholic steatohepatitis (NASH), referring to MASLD with histological evidence of steatohepatitis characterized by steatosis, hepatocellular ballooning, and lobular inflammation [1, 14].

2.2.4. Metabolic and Alcohol-Associated Liver Disease (MetALD)

A new diagnostic category describing individuals with MASLD who consume alcohol beyond the thresholds previously used to define NAFLD (140-350 g/week for females and 210-420 g/week for males) [1, 15]. This category acknowledges the synergistic effects of metabolic dysfunction and moderate alcohol consumption on liver disease progression.

2.2.5. Cryptogenic Steatotic Liver Disease

Reserved for individuals with hepatic steatosis who do not meet criteria for MASLD and have no other identifiable cause [1, 2].

2.3. Advantages of the New Nomenclature

The transition to MASLD offers several intended clinical and research advantages. First, the affirmative, inclusion-based diagnostic criteria eliminate the need for exclusionary diagnoses, simplifying clinical practice [3, 4]. Second, the terminology emphasizes the metabolic foundations of disease pathogenesis, aligning diagnostic nomenclature with therapeutic targets [5, 16]. Third, non-stigmatizing language is intended to improve patient engagement, reduce psychological burden, and enhance healthcare-seeking behavior. However, prospective studies are needed to validate these anticipated benefits [3, 17].

Importantly, comparative analyses demonstrate that MASLD criteria capture approximately 99% of individuals previously diagnosed with NAFLD, ensuring continuity of natural history data, clinical trial applicability, and biomarker validation [18, 19]. The new nomenclature does not alter histological staging systems or modify the definition of steatohepatitis, preserving the relevance of decades of NASH-focused research [1, 14].

3. Epidemiology and Clinical Burden of MASLD

MASLD represents the most prevalent chronic liver condition worldwide, affecting an estimated 30% of the global adult population [6, 20]. Prevalence varies geographically, with the highest rates observed in South America (44.4%), the Middle East (32%), and Asia (29.6%) [20, 21]. In industrialized nations, MASLD prevalence parallels obesity rates, with approximately 25-30% of adults in North America and Europe affected [21, 22].

The condition demonstrates a particular predilection for individuals with metabolic syndrome components. Among patients with type 2 diabetes mellitus, MASLD prevalence reaches 55-70%, while obese individuals exhibit prevalence rates of 70-90% [23, 24]. Notably, 7-20% of MASLD cases occur in non-obese or lean individuals, highlighting the complex pathophysiology beyond simple weight-related mechanisms [25, 26].

Progressive fibrosis develops in approximately 20-30% of individuals with MASLD, with 10-15% advancing to cirrhosis over 10-20 years [27]. The presence of metabolic dysfunction-associated steatohepatitis (MASH) significantly accelerates fibrosis progression, with advanced fibrosis developing in 25-35% of MASH patients [28, 29].

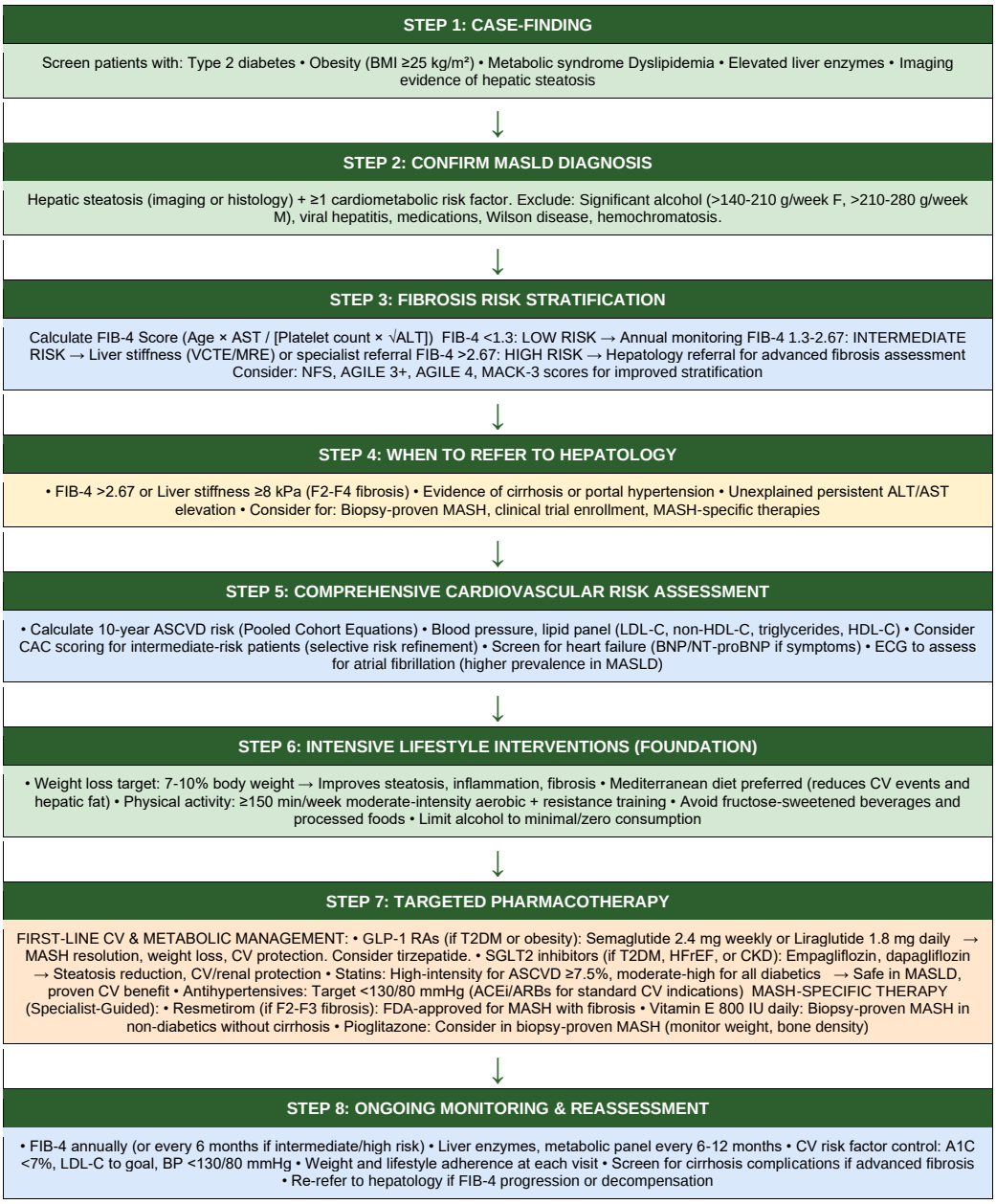

Figure 1: Integrated Management Algorithm for MASLD in Internal Medicine Practice.
Abbreviations: MASLD, metabolic dysfunction-associated steatotic liver disease; BMI, body mass index; FIB-4, Fibrosis-4 Index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; VCTE, vibration-controlled transient elastography; MRE, magnetic resonance elastography; NFS, NAFLD fibrosis score; MASH, metabolic dysfunction-associated steatohepatitis; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; BNP, B-type natriuretic peptide; ECG, electrocardiogram; T2DM, type 2 diabetes mellitus; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose cotransporter-2; HFrEF, heart failure with reduced ejection fraction; CKD, chronic kidney disease; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; FDA, Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; BP, blood pressure; A1C, hemoglobin A1C.

Critically, cardiovascular disease represents the leading cause of mortality in MASLD patients, accounting for approximately 40-50% of deaths, far exceeding liver-related mortality, which accounts for only 5-15% of deaths in non-cirrhotic MASLD [30, 31]. This epidemiological profile underscores the primacy of cardiovascular risk management in MASLD care paradigms.

4. Pathophysiological Mechanisms Linking MASLD and Cardiovascular Disease

The liver-heart axis in MASLD is characterized by complex, bidirectional interactions mediated through multiple overlapping pathophysiological mechanisms [32].

4.1. Insulin Resistance and Metabolic Dysregulation

Insulin resistance is a cornerstone pathophysiological feature linking MASLD to cardiovascular disease [33, 34]. Hepatic steatosis both

results from and perpetuates systemic insulin resistance through the release of pro-inflammatory cytokines, altered lipoprotein metabolism, and the secretion of a diverse repertoire of hepatokines – liver-derived circulating proteins that mediate inter-organ crosstalk across the liver-heart axis. These hepatokines can be broadly organized by their predominant downstream effects. Among those with primary metabolic relevance, fibroblast growth factor 21 (FGF21) is paradoxically elevated in MASLD despite its physiological role in promoting fatty acid oxidation and insulin sensitization, a state of FGF21 resistance analogous to leptin resistance in obesity. Fetuin-A and fetuin-B, both upregulated in hepatic steatosis, impair insulin receptor signaling and promote systemic insulin resistance, with fetuin-A additionally serving as an endogenous inhibitor of the insulin receptor tyrosine kinase [35]. Selenoprotein P, a hepatokine elevated in MASLD and type 2 diabetes, impairs insulin signaling in skeletal muscle and the myocardium and has been independently associated with cardiovascular risk. Sex hormone-binding globulin (SHBG), whose hepatic synthesis is suppressed by insulin resistance and hepatic fat accumulation, serves as an inverse biomarker of metabolic syndrome severity and has been associated with incident type 2 diabetes and cardiovascular disease risk. Among hepatokines with more direct vascular and lipid-trafficking relevance, angiopoietin-like proteins 3, 4, and 8 (ANGPTL3, ANGPTL4, ANGPTL8) regulate lipoprotein lipase activity and plasma triglyceride clearance; their dysregulation in MASLD contributes to atherogenic dyslipidemia and has positioned ANGPTL3 in particular as an emerging therapeutic target in cardiometabolic disease. Hepassocin, a hepatocyte-derived growth factor, promotes hepatic steatosis by upregulating lipogenic pathways and has been associated with endothelial dysfunction and early atherosclerosis. However, its precise role in the MASLD-cardiovascular axis remains to be characterized. Collectively, this hepatokine network illustrates how the steatotic liver actively remodels systemic metabolic and vascular homeostasis, extending its pathological influence well beyond the hepatic parenchyma [35, 36].

A meta-analysis involving over 500,000 participants demonstrated that insulin resistance, measured by the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR), significantly elevates the risk of atherosclerotic cardiovascular disease, with each 1 standard deviation increase in HOMA-IR correlating with a 1.46-fold higher risk of developing atherosclerotic cardiovascular disease [37]. Similarly, HOMA-IR scores have been independently associated with altered left ventricular relaxation and diastolic dysfunction, affecting up to 50% of patients with type 2 diabetes [38, 39].

4.2. Chronic Low-Grade Inflammation

Hepatic steatosis triggers activation of innate immune pathways, particularly through Kupffer cells and hepatic stellate cells, resulting in production and systemic release of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), and C-reactive protein (CRP) [40, 41]. These inflammatory mediators promote endothelial dysfunction, accelerate atherosclerosis, and contribute to myocardial remodeling [42, 43].

The inflammatory phase of MASLD, characterized by steatohepatitis (MASH), demonstrates particularly robust systemic inflammatory activity. Inflammatory spillover from the liver affects distant organs, including the heart, skeletal muscle, and kidneys, contributing to the multisystem impact of disease [44, 45].

4.3. Oxidative Stress and Lipotoxicity

Excess reactive oxygen species generated in lipid-laden hepatocytes and activated macrophages contribute to mitochondrial dysfunction, lipid peroxidation, and cytokine release [46, 47]. This oxidative milieu fosters the formation of oxidized low-density lipoprotein (LDL) and perpetuates vascular inflammation. Studies have linked markers of oxidative stress in MASLD with increased carotid intima-media thickness and coronary artery calcification, established precursors of clinical cardiovascular disease [48, 49].

Lipotoxicity, resulting from the accumulation of toxic lipid species including ceramides, diacylglycerols, and free fatty acids, directly impairs cardiomyocyte function and promotes cardiac fibrosis [50, 51].

4.4. Atherogenic Dyslipidemia

MASLD is characterized by a distinctive atherogenic lipid profile including elevated triglycerides, increased small dense LDL particles, reduced HDL cholesterol, and elevated apolipoprotein B [52, 53]. This dyslipidemia results from hepatic overproduction of very-low-density lipoproteins (VLDL), impaired lipoprotein clearance, and altered apolipoprotein metabolism [54, 55].

The atherogenic dyslipidemia associated with MASLD independently predicts cardiovascular events beyond traditional Framingham risk factors [56, 57].

4.5. Gut-Liver-Heart Axis

Emerging evidence highlights the roles of gut microbiome dysbiosis, increased intestinal permeability, and bacterial translocation in the pathogenesis of MASLD and cardiovascular disease [58, 59]. Patients with MASLD exhibit altered gut microbial composition, with increased abundance of pro-inflammatory taxa, including Enterobacteriaceae and Proteobacteria, and decreased abundance of beneficial commensals, including Faecalibacterium prausnitzii and Akkermansia muciniphila [60, 61].

Lipopolysaccharides (LPS) derived from gut bacteria traverse the compromised intestinal barrier, reach the liver via portal circulation, and activate toll-like receptor 4 (TLR4) signaling, triggering hepatic and systemic inflammation [62, 63]. Elevated circulating LPS levels have been associated with both MASLD severity and cardiovascular events [64, 65]. A particularly well-characterized gut-derived metabolite linking hepatic and cardiovascular pathology is trimethylamine N-oxide (TMAO). Generated when gut bacteria metabolize dietary choline, phosphatidylcholine, and L-carnitine to trimethylamine (TMA), which is subsequently oxidized to TMAO by hepatic flavin-containing monooxygenase 3 (FMO3), circulating TMAO levels reflect the combined influence of dietary substrate availability, gut microbial composition, and hepatic oxidative capacity – all of which are altered in MASLD [59]. Elevated TMAO has been independently associated with accelerated atherosclerosis through promotion of macrophage foam cell formation and impaired reverse cholesterol transport, with enhanced platelet hyperreactivity and thrombotic risk, and with adverse cardiac remodeling and incident heart failure, including heart failure with preserved ejection fraction [64]. Patients with MASLD demonstrate elevated circulating TMAO levels compared to matched controls, and TMAO concentrations correlate with hepatic fibrosis severity, suggesting that progressive liver dysfunction amplifies TMAO generation and systemic vascular exposure [62]. While direct interventional data in MASLD remain limited, TMAO biology provides a mechanistically coherent link between gut dysbiosis, hepatic metabolic dysfunction, and the full spectrum of cardiovascular manifestations observed in this population – spanning atherosclerosis, thrombosis, and heart failure – reinforcing the clinical importance of the gut-liver-heart axis.

4.6. Hepatic Fibrosis and Cardiovascular Risk

Hepatic fibrosis stage has emerged as a critical determinant of cardiovascular risk in MASLD, often surpassing the predictive value of steatosis or steatohepatitis alone [66, 67]. Advanced fibrosis (stage F3-F4) is independently associated with increased cardiovascular events, cardiovascular mortality, and all-cause mortality [68, 69].

The mechanisms linking hepatic fibrosis to cardiovascular disease remain incompletely understood but likely involve persistent systemic inflammation, endothelial dysfunction, enhanced platelet activation, and altered hepatic synthesis of cardiovascular-protective proteins [70, 71].

4.7. Genetic Determinants and the Discordant Phenotype Problem

Common genetic variants exert substantial influence on MASLD susceptibility, fibrosis progression, and – critically – cardiovascular risk profiles, often in discordant directions, with direct clinical relevance for internists. The most studied variant, PNPLA3 I148M (rs738409), encodes a gain-of-function substitution in patatin-like phospholipase domain-containing protein 3 that impairs hepatic lipid droplet remodeling. Carriers of the G allele demonstrate accelerated hepatic steatosis, steatohepatitis, fibrosis, and hepatocellular carcinoma risk, yet paradoxically do not appear to carry a proportionally elevated cardiovascular risk, possibly because the variant promotes hepatic lipid retention rather than dyslipidemic spillover into the systemic circulation [72, 73].

The TM6SF2 E167K variant (rs58542926) illustrates this dissociation most strikingly. Loss-of-function of transmembrane 6 superfamily member 2 reduces hepatic VLDL secretion, resulting in hepatic lipid accumulation and accelerated fibrosis, while simultaneously lowering circulating triglycerides and LDL cholesterol – a profile associated with reduced atherosclerotic cardiovascular disease risk despite more severe liver disease [70, 73]. This TM6SF2 paradox exemplifies why genetic background can uncouple the liver-heart axis, and why cardiovascular risk cannot be assumed to track linearly with hepatic disease severity in all patients.

HSD17B13 loss-of-function variants confer hepatoprotection by reducing hepatic inflammatory activity and fibrosis progression, and have attracted interest as therapeutic targets, though their effect on cardiovascular risk remains under investigation [73, 74]. MBOAT7 variants similarly promote hepatic steatosis and fibrosis through altered phosphatidylinositol remodeling, with an emerging but incompletely characterized cardiometabolic profile [73].

For internists, the practical implication is that patients with discordant phenotypes – severe liver disease but favorable lipid profiles, or vice versa – may harbor underlying genetic architecture that modifies standard cardiovascular risk predictions. While routine genetic testing is not currently recommended in clinical practice, awareness of these variants helps explain phenotypic heterogeneity among patients with MASLD. It underscores the need for individualized rather than uniform cardiovascular risk assessment.

4.8. The Reverse Pathway: Cardiac Dysfunction and Congestive Hepatopathy

While the predominant focus of the liver-heart axis in MASLD literature is the forward pathway from hepatic metabolic dysfunction to cardiovascular disease, the reverse pathway – wherein primary cardiac dysfunction drives progressive hepatic injury – is of equal clinical importance for internists and represents a distinct but intersecting disease process [11, 71].

4.8.1. Hemodynamic Mechanisms

Right-sided heart failure, whether arising de novo or as a consequence of advanced left ventricular dysfunction, generates sustained elevation of central venous and hepatic venous pressures. This increased back-pressure is transmitted directly to the hepatic sinusoids via the inferior vena cava and hepatic veins, resulting in sinusoidal congestion, hepatocellular hypoxia, and zone 3 (centrilobular) necrosis – the histological hallmark of congestive hepatopathy [11, 71]. In parallel, reduced cardiac output impairs hepatic arterial perfusion, creating a dual insult of venous congestion and arterial ischemia that is particularly injurious in the setting of acute decompensation. Elevated right atrial pressure also impairs portal venous return, contributing to splanchnic congestion, gut barrier dysfunction, and bacterial translocation, which may further amplify systemic inflammation [58, 63].

4.8.2. Congestive Hepatopathy and Cardiac Cirrhosis

Chronic, sustained hepatic venous hypertension – most commonly seen in patients with heart failure with reduced ejection fraction, constrictive pericarditis, severe tricuspid regurgitation, or Fontan circulation – drives progressive hepatic fibrosis by activating hepatic stellate cells in response to persistent sinusoidal pressure and hypoxia [70, 71]. This process, termed congestive hepatopathy, exists on a spectrum from mild centrilobular fibrosis to frank cardiac cirrhosis, the latter carrying its own risks of portal hypertension, hepatic synthetic dysfunction, variceal bleeding, and hepatocellular carcinoma [71]. The fibrosis pattern of cardiac cirrhosis is characteristically reversed to that of MASLD – beginning in zone 3 (centrilobular) rather than zone 1 (periportal) – a distinction of diagnostic importance when evaluating liver biopsy specimens in patients with coexisting cardiac and metabolic disease [70].

4.8.3. Portal Hemodynamics and Clinical Consequences

As congestive hepatopathy progresses, portal hypertension may develop even in the absence of advanced parenchymal fibrosis, driven primarily by elevated hepatic venous outflow resistance rather than intrahepatic architectural distortion [71]. Clinically, this manifests as ascites, peripheral edema, and splenomegaly – findings that may be incorrectly attributed to cardiac failure alone, delaying recognition of the hepatic contribution. Hepatic synthetic function, reflected by prolonged prothrombin time, hypoalbuminemia, and hyperbilirubinemia, is impaired in advanced congestive hepatopathy and carries independent prognostic significance in heart failure patients beyond standard cardiac biomarkers [11, 71]. Serum aminotransferases are typically mildly elevated in chronic congestive hepatopathy. Still, they may rise sharply – occasionally mimicking acute hepatitis – during episodes of acute hemodynamic decompensation, a pattern sometimes termed ischemic hepatitis or shock liver [70, 71].

4.8.4. Clinical Implications for Internists

For internists, several practical points follow from recognition of the reverse pathway. First, liver function abnormalities in patients with known heart failure should not be reflexively attributed to medications or incidental hepatic disease; a hemodynamic contribution should be systematically considered, particularly when right-sided pressures are elevated [11, 71]. Second, the coexistence of MASLD and congestive hepatopathy in the same patient – increasingly common given the shared cardiometabolic substrate – creates diagnostic complexity, as fibrosis on non-invasive testing or biopsy may reflect both metabolic and congestive mechanisms [70]. Third, optimization of cardiac hemodynamics – through guideline-directed medical therapy, diuresis, device therapy, or valve intervention – represents the primary therapeutic lever for congestive hepatopathy, and hepatic parameters frequently improve with successful cardiac

management [71]. Fourth, in patients being evaluated for advanced heart failure therapies, including left ventricular assist devices or cardiac transplantation, accurate hepatic assessment is essential, as significant hepatic fibrosis or cardiac cirrhosis may influence candidacy and post-procedural outcomes [11, 71].

5. Cardiovascular Manifestations of MASLD

5.1. Coronary artery disease and Myocardial Infarction

Multiple epidemiological studies demonstrate robust associations between MASLD and coronary artery disease [75, 76]. Meta-analyses report that MASLD increases the risk of coronary artery disease by 1.5-2.0-fold after adjustment for traditional cardiovascular risk factors [32, 77]. The association strengthens with disease severity, with MASH and advanced fibrosis conferring a higher risk than simple steatosis [78, 79].

MASLD patients exhibit increased coronary artery calcification scores, higher prevalence of vulnerable plaque morphology, and greater extent of multivessel coronary disease compared to matched controls [80, 81]. Importantly, myocardial infarction risk increases progressively with the stage of hepatic fibrosis, underscoring the importance of fibrosis assessment in cardiovascular risk stratification [68, 82].

5.2. Heart Failure

MASLD demonstrates particularly strong associations with heart failure, especially heart failure with preserved ejection fraction (HFpEF) [83, 84]. Meta-analytic evidence indicates that MASLD increases heart failure risk by approximately 1.5-fold, with higher relative risks for HFpEF compared to heart failure with reduced ejection fraction (HFrEF) [85, 86].

Magnetic resonance imaging studies reveal structural and functional cardiac alterations in MASLD patients, including increased left ventricular mass, concentric remodeling, impaired diastolic relaxation, and reduced myocardial strain, even in the absence of clinically evident cardiac disease [87, 88]. Increased epicardial adipose tissue thickness, commonly observed in MASLD, promotes cardiac dysfunction through pro-inflammatory cytokine production and direct lipotoxic effects on myocardium [89, 90].

5.3. Atrial Fibrillation

Emerging evidence links MASLD to increased atrial fibrillation prevalence and incidence [91, 92]. The inflammatory milieu characteristic of MASH may foster atrial electrical remodeling, promoting arrhythmogenesis [72, 93]. Meta-analyses demonstrate that MASLD increases atrial fibrillation risk by approximately 1.4-fold, with risk amplification in patients with more severe hepatic disease [94, 95].

5.4. Stroke

Several observational studies report associations between MASLD and increased stroke risk, both ischemic and hemorrhagic subtypes [96, 97]. MASLD patients demonstrate higher carotid intima-media thickness, increased carotid plaque prevalence, and greater plaque vulnerability compared to controls. Meta-analytic estimates suggest MASLD increases stroke risk by approximately 1.3-1.5-fold [98, 99].

5.5. Cardiovascular Mortality

Critically, MASLD significantly increases cardiovascular mortality risk, which represents the leading cause of death in this population [68, 100]. Meta-analyses including over 9 million participants demonstrate that MASLD increases cardiovascular mortality risk by approximately 1.6-fold compared to individuals without MASLD [101, 102]. Risk escalates with disease severity, with MASH and advanced fibrosis conferring substantially higher cardiovascular mortality compared to simple steatosis [103, 104].

6. Diagnostic Considerations and Risk Stratification

6.1. Establishing the Diagnosis of MASLD

Diagnosis of MASLD requires documentation of hepatic steatosis through imaging or histology, plus verification of at least one cardiometabolic risk factor [1, 13]. Hepatic steatosis can be identified through multiple modalities:

6.1.1. Imaging Modalities

- Ultrasonography: Widely available, cost-effective first-line modality; sensitivity 60–94% for detecting $\geq$ 20–30% hepatic steatosis [105, 106].
- Controlled Attenuation Parameter (CAP): Adjunct to transient elastography; provides quantitative steatosis assessment [107, 108].
- Magnetic Resonance Imaging-Proton Density Fat Fraction (MRI-PDFF): Gold standard for non-invasive steatosis quantification; high accuracy for detecting $\geq$ 5% hepatic fat [109, 110].
- Computed Tomography: Can detect moderate-to-severe steatosis; radiation exposure limits routine use [111, 112].

6.1.2. Histological Assessment

Liver biopsy remains the reference standard for diagnosing MASH and staging fibrosis, although its invasive nature limits its routine use [113, 114].

6.2. Case-Finding Strategies

Current guidelines recommend case-finding for MASLD with liver fibrosis using non-invasive tests in high-risk populations, particularly individuals with type 2 diabetes, obesity with additional metabolic risk factors, abnormal liver enzymes, or radiological signs of hepatic steatosis [115, 116].

6.3. Fibrosis Assessment

Given the critical prognostic importance of hepatic fibrosis for both hepatic and cardiovascular outcomes, accurate assessment of fibrosis is essential [117, 118]. Non-invasive tools have evolved substantially, and a sequential, stepwise strategy combining simple blood-based scores with imaging-based elastography – and increasingly with newer composite scores – now allows the majority of patients to be risk-stratified without liver biopsy.

6.3.1. Non-Invasive Fibrosis Assessment

1. **Fibrosis-4 Index (FIB-4)**: Calculated using age, AST, ALT, and platelet count; cutoffs < 1.3 (or < 2.0 for age $\geq$ 65 years) reliably exclude advanced fibrosis; values > 2.67 suggest high probability of advanced fibrosis and warrant further evaluation [119, 120]. FIB-4 remains the recommended first-line triage tool in primary care and general internal medicine settings, given its simplicity, zero additional cost, and robust validation across diverse populations.
2. **NAFLD Fibrosis Score (NFS)**: Incorporates age, BMI, hyperglycemia, platelet count, albumin, and AST/ALT ratio; cutoff < -1.455 excludes advanced fibrosis; score > 0.676 suggests advanced fibrosis [121, 122]. NFS performs comparably to FIB-4 as a first-line triage instrument, though its BMI dependency may limit precision in patients with extreme obesity.

3. **Transient Elastography (TE)**: Measures liver stiffness as a surrogate for fibrosis; cutoff < 8 kPa excludes advanced fibrosis; values > 12–14 kPa suggest advanced fibrosis or cirrhosis [123, 124]. TE is well-validated, widely available, and reproducible, but carries important technical limitations in patients with BMI > 35 kg/m^2, narrow intercostal spaces, or significant ascites, in whom probe failure or unreliable readings are substantially more frequent. In these patients, an alternative elastography modality should be prioritized rather than accepting an indeterminate TE result.
4. **Magnetic Resonance Elastography (MRE)**: MRE measures liver stiffness through propagation of mechanical shear waves quantified by MRI, and is currently the most accurate non-invasive modality for fibrosis staging across the full spectrum from F0 to F4 [109, 110]. Critically, MRE is not subject to the BMI-related technical failures that limit TE, making it the preferred elastography modality in patients with significant obesity, prior indeterminate TE, or where precise fibrosis staging will directly influence management decisions, such as eligibility for MASH-specific pharmacotherapy or advanced heart failure evaluation. The principal limitations of MRE are cost, scanner availability, and the presence of hepatic iron, which can confound stiffness measurements [109, 110].
5. **Enhanced Liver Fibrosis (ELF) Score**: Blood-based test measuring hyaluronic acid, procollagen III N-terminal peptide, and tissue inhibitor of metalloproteinases-1; score < 9.8 excludes advanced fibrosis [125, 126]. ELF performs well as a second-line confirmatory test and is particularly useful when elastography is unavailable or technically limited.
6. **AGILE 3+ and AGILE 4**: These newer composite scores combine FIB-4 with liver stiffness measured by TE to produce a single integrated probability estimate for advanced fibrosis (AGILE 3+) or cirrhosis (AGILE 4) [127, 128]. By incorporating both biochemical and elastographic information, AGILE scores substantially reduce the proportion of patients falling into the indeterminate zone that characterizes FIB-4 or TE alone – a clinically important advance, as indeterminate results currently represent the most common reason for unnecessary hepatology referral or biopsy in primary care pathways. Validation studies demonstrate that sequential use of FIB-4 followed by AGILE 3+ can correctly rule in or rule out advanced fibrosis in a larger proportion of patients than any single test, with only a minority requiring liver biopsy for definitive staging [127, 128].
7. **MACK-3**: A composite score integrating serum markers of cell death (cytokeratin-18 fragments), fibrogenesis (PRO-C3, a marker of type III collagen synthesis), and standard biochemistry, MACK-3 is specifically designed to identify patients with active MASH and significant fibrosis – the population most likely to benefit from pharmacological intervention [126, 127]. Its utility lies particularly in distinguishing patients with simple steatosis from those with progressive steatohepatitis and fibrosis, a distinction that blood-based scores and elastography alone cannot reliably make, and it may help prioritize biopsy or treatment initiation in patients with borderline fibrosis scores.

6.3.2. Risk Stratification Pathway

Current best practice supports a sequential stratification approach. In primary care and general internal medicine, FIB-4 serves as the universal first-line triage tool. Patients with low FIB-4 values can be reassured and monitored, while those with high values should be referred to hepatology. The critical challenge lies in the indeterminate FIB-4 range (1.3 – 2.67), which encompasses a substantial proportion of patients. In this group, second-line evaluation with TE is appropriate when technically feasible; where TE is limited by obesity or yields unreliable results, MRE should be used. AGILE 3+ can be applied to integrate FIB-4 and TE results and further reduce the indeterminate fraction. MACK-3 may add value in patients in whom distinguishing active MASH from simple steatosis would alter management decisions, particularly when considering MASH-specific pharmacotherapy. Patients with evidence of advanced fibrosis on any validated pathway warrant referral to hepatology for comprehensive management and consideration of liver biopsy [129, 130].

6.4. Cardiovascular Risk Assessment

All MASLD patients require systematic cardiovascular risk evaluation incorporating [131, 132]:

1. Traditional risk factor assessment: Lipid profile, blood pressure, diabetes status, smoking history, family history of premature cardiovascular disease
2. Calculation of 10-year atherosclerotic cardiovascular disease risk using validated algorithms (e.g., Pooled Cohort Equations)
3. Evaluation for subclinical atherosclerosis through carotid ultrasound or coronary artery calcium scoring in intermediate-risk patients
4. Assessment of hepatic fibrosis stage, recognizing advanced fibrosis as a cardiovascular risk amplifier

7. Management Strategies: An Integrated Approach

7.1. Lifestyle Modification: The Cornerstone of Therapy

Lifestyle intervention targeting weight reduction, dietary modification, and increased physical activity represents the foundation of MASLD management [133, 134].

7.1.1. Weight Loss Targets

Weight reduction of 3-5% improves hepatic steatosis, while 7-10% weight loss is required to improve steatohepatitis and fibrosis [135, 136]. Greater weight loss (≥ 10%) yields more robust benefits, including regression of fibrosis [137, 138].

7.1.2. Dietary Recommendations

Mediterranean diet patterns emphasizing monounsaturated fats, omega-3 fatty acids, whole grains, fruits, vegetables, and limited processed foods improve both hepatic and cardiovascular parameters [139, 140]. Reduction of fructose-containing beverages and processed carbohydrates benefits hepatic steatosis and metabolic profiles [141, 142].

7.1.3. Physical Activity

Regular aerobic exercise (150-200 minutes of moderate-intensity activity weekly) and resistance training improve hepatic steatosis, insulin sensitivity, and cardiovascular fitness, independent of weight loss [143, 144].

7.2. Pharmacological Management of Cardiometabolic Risk Factors

7.2.1. Antidiabetic Agents

1. **Metformin**: While not specifically approved for MASLD/MASH treatment, metformin provides cardiovascular protection in diabetic patients and may modestly improve hepatic parameters [145, 146].

2. **Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) and Incretin-Based Combination Therapies**: Incretin-based therapies represent the most rapidly evolving pharmacological class in MASLD management, and internists will increasingly encounter patients on dual- and triple-receptor agonists whose hepatic and cardiovascular effects extend well beyond traditional glycemic indications.
Among selective GLP-1 RAs, liraglutide 1.8 mg daily demonstrated MASH resolution in 39% of patients, compared with 9% with placebo in the LEAN trial, predominantly in patients with type 2 diabetes, and established cardiovascular outcome benefits in the LEADER trial [147, 148]. Semaglutide 2.4 mg weekly achieved MASH resolution without worsening of fibrosis in 59% versus 17% with placebo in the STEP-MASH trial, and subsequently received FDA accelerated approval for MASH in August 2025 based on the ESSENCE trial; cardiovascular outcome data from FLOW and SELECT support its cardiometabolic benefit profile [148, 149]. These agents promote substantial weight loss of 10–15%, improve glycemic control, reduce systemic inflammation, and reduce major adverse cardiovascular events, making them a logical first-choice pharmacological option in MASLD patients with type 2 diabetes or obesity [147–149].
Tirzepatide, a dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist (GIP/GLP-1 RA), achieves superior weight loss of 20–22% and metabolic improvements compared to selective GLP-1 RAs in head-to-head and placebo-controlled trials [147, 149]. The SURMOUNT-NASH trial has demonstrated significant reductions in hepatic steatosis and emerging signals of improved fibrosis with tirzepatide, with full histological outcome data anticipated imminently; cardiovascular outcome data from the SURPASS-CVOT program are maturing [148, 149]. For internists, tirzepatide represents a clinically available option with a compelling cardiometabolic profile. However, MASH-specific regulatory approval remained pending at the time of writing, and prescribing should reflect current approved indications.
Triple receptor agonists – most notably retatrutide, a GIP/GLP-1/glucagon receptor triagonist – represent the next frontier of incretin-based therapy and are entering phase 3 development following striking phase 2 signals. Retatrutide achieved mean weight loss exceeding 24% at 48 weeks in phase 2 trials, with substantial reductions in hepatic fat fraction and favorable cardiometabolic biomarker profiles, including triglyceride lowering and improvements in insulin sensitivity [73, 74]. Phase 2 data for cotadutide, a GLP-1/glucagon dual agonist with direct antifibrotic signaling through hepatic glucagon receptors, demonstrated reductions in hepatic steatosis and liver stiffness in MASLD patients with type 2 diabetes [73, 74]. While phase 3 histological and cardiovascular outcome data for triple agonists are not yet available, internists should be aware of this emerging class, as patients will increasingly inquire about it and early real-world use outside of trials is likely to precede full regulatory evaluation. Appropriate caution is warranted: the magnitude of weight loss does not automatically translate into fibrosis regression or a reduction in cardiovascular events, and long-term safety data for the glucagon receptor agonist component – including effects on bone density, heart rate, and blood pressure – require further characterization in dedicated outcome trials [73, 74].
Across all incretin-based therapies, women, older adults, and patients with lean MASLD were underrepresented in pivotal trials, limiting the generalizability of efficacy and safety conclusions to these populations. Sex-stratified and ethnicity-stratified outcome data from ongoing trials will be important to inform individualized prescribing decisions.
3. **Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i)**: SGLT2 inhibitors improve hepatic steatosis, reduce cardiovascular events, and demonstrate favorable effects on heart failure outcomes [150, 151].
4. **Pioglitazone**: Thiazolidinediones improve insulin sensitivity and demonstrate histological benefits in MASH, including steatohepatitis resolution and potential fibrosis improvement, though weight gain, fluid retention, and bone density concerns limit use [152, 153].
5. **Vitamin E (α-tocopherol)**: Vitamin E 800 IU daily is recommended by multiple society guidelines for biopsy-proven MASH in non-diabetic patients without cirrhosis. The PIVENS trial demonstrated MASH resolution in 36% of patients, compared with 21% with placebo, though fibrosis improvement was not significant. Use in diabetic patients remains controversial, given possible increased cardiovascular and prostate cancer risks, and routine supplementation is not recommended without biopsy confirmation of MASH [152, 153].

7.2.2. Lipid-Lowering Therapy

Statins are safe in patients with MASLD and should be prescribed according to cardiovascular risk-stratification guidelines [154, 155]. Statins reduce cardiovascular events without worsening liver disease and may provide modest hepatoprotective effects. Combination therapy with ezetimibe or PCSK9 inhibitors can be used for patients who do not achieve lipid targets [156, 157].

7.2.3. Antihypertensive Therapy

Blood pressure control follows standard guidelines. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are used for their established cardiovascular and renal indications. Observational data suggest possible hepatoprotective effects, though these agents are not recommended specifically for antifibrotic benefit in MASLD, given the lack of robust randomized controlled trial evidence [158, 159].

7.3. Emerging MASLD-Specific Pharmacotherapies

The therapeutic landscape for MASH-specific pharmacotherapy has evolved rapidly. Resmetirom (Rezdiffra), a thyroid hormone receptor-beta agonist, received FDA accelerated approval in March 2024 for the treatment of MASH with moderate-to-advanced fibrosis (F2 – F3), based on the MAESTRO-NASH trial demonstrating MASH resolution in 26% versus 10% with placebo and $\geq$ 1-stage fibrosis improvement in 24% versus 14%; confirmatory cardiovascular outcome data are pending [160, 161]. Subsequently, in August 2025, semaglutide 2.4 mg weekly (Wegovy) received FDA accelerated approval for MASH, based on the ESSENCE trial demonstrating histological benefit in patients with obesity-related MASH [149]. Regulatory status for both agents varies by jurisdiction – neither had received full European Medicines Agency (EMA) approval for a MASH-specific indication at the time of writing – and clinicians should consult current national regulatory guidance, as approvals in this area are actively evolving [73, 74]. Several additional agents remain in late-stage clinical development:

1. **Obeticholic acid**: Farnesoid X receptor agonist showing antifibrotic effects in phase 3 trials, though cardiovascular safety concerns and regulatory decisions require ongoing clarification [162, 163].

2. **Combination therapies**: Trials evaluating agents targeting multiple pathophysiological pathways simultaneously show promise and may represent the next frontier in MASH treatment [164, 165].

7.4. Multidisciplinary Care Coordination

Optimal MASLD management necessitates multidisciplinary collaboration involving internists, hepatologists, endocrinologists, cardiologists, dietitians, and behavioral health specialists [147, 166]. Internists serve critical roles in:

1. Initial identification and diagnosis of MASLD
2. Comprehensive cardiovascular risk assessment and management
3. Optimization of cardiometabolic risk factors
4. Facilitation of lifestyle modifications through counseling and referrals
5. Appropriate specialty referrals for advanced disease
6. Long-term disease monitoring and prevention of complications

The integrated stepwise management algorithm for MASLD in internal medicine practice is illustrated in **(Figure 1)**.

8. Special Populations and Considerations

8.1. Type 2 Diabetes Mellitus

Patients with concurrent MASLD and type 2 diabetes represent a particularly high-risk population requiring intensive management [167, 168]. These individuals demonstrate accelerated fibrosis progression, higher cardiovascular event rates, and increased mortality compared to MASLD patients without diabetes [169, 170]. Prioritization of GLP-1 receptor agonists and SGLT2 inhibitors offers dual benefits for glycemic control, cardiovascular protection, and hepatic improvement [171, 172].

8.2. Lean MASLD

Approximately 7-20% of MASLD cases occur in non-obese individuals (BMI <25 kg/m² in non-Asian populations; <23 kg/m² in Asian populations) [100, 173]. Lean MASLD patients demonstrate distinct metabolic profiles, genetic predispositions, and potentially different cardiovascular risk profiles compared to obese MASLD patients [174, 175]. These individuals warrant equally aggressive cardiovascular risk modification despite normal body weight.

8.3. Elderly Patients

Advanced age represents both a risk factor for MASLD development and a contributor to accelerated fibrosis progression [176, 177]. Elderly MASLD patients face elevated cardiovascular risks and require careful medication selection considering comorbidities, polypharmacy, and altered pharmacokinetics [178, 179].

8.4. Sex Differences, Hormonal Influences, and MASLD

Sex exerts a profound and clinically underappreciated influence on MASLD prevalence, histological severity, fibrosis trajectory, cardiovascular risk profile, and likely treatment response – differences that internists managing cardiometabolic disease must recognize to avoid uniform approaches that may inadequately serve female patients in particular.

8.4.1. Prevalence and Histological Patterns

Premenopausal women consistently have lower MASLD prevalence than age-matched men, with global estimates suggesting a male-to-female ratio of approximately 2:1 in reproductive-age cohorts [6, 20]. This relative protection is largely attributed to the metabolic and vascular effects of endogenous estrogen, which promote favorable adipose tissue distribution, enhance hepatic insulin sensitivity, suppress de novo lipogenesis, and exert anti-inflammatory effects through estrogen receptor-alpha signaling in hepatocytes and Kupffer cells [176, 177]. Despite lower prevalence, premenopausal women who develop MASLD tend to present with less severe steatosis but comparable or greater lobular inflammation than men, suggesting that inflammatory pathways may be activated at lower thresholds of hepatic fat accumulation in this population [176].

8.4.2. Menopause as an Inflection Point

The menopausal transition represents a critical inflection point in female MASLD risk. Estrogen withdrawal at menopause drives visceral adiposity redistribution, worsening insulin resistance, dyslipidemia characterized by rising LDL and triglycerides and falling HDL, and heightened systemic inflammation. This cardiometabolic profile closely mirrors the metabolic underpinnings of MASLD progression [177, 179]. Postmenopausal women demonstrate MASLD prevalence and severity approaching or exceeding that of age-matched men, with accelerated fibrosis progression rates observed in cohort studies following women through the menopausal transition [176, 177]. Early menopause, defined as onset before age 45, has been independently associated with higher MASLD prevalence and more advanced fibrosis, underscoring the dose-dependent hepatoprotective role of cumulative estrogen exposure [177]. Surgical menopause confers particularly elevated risk, with bilateral oophorectomy associated with accelerated steatohepatitis and fibrosis progression in observational data [176, 179].

The cardiovascular implications of this hormonal inflection are equally significant. Postmenopausal women with MASLD face a compounded cardiovascular risk burden: estrogen loss independently accelerates atherosclerosis and increases susceptibility to HFpEF, while MASLD-driven insulin resistance, atherogenic dyslipidemia, and systemic inflammation add further risk layers that may not be fully captured by standard Framingham-based risk calculators calibrated predominantly on male cohorts [131, 132, 177]. Internists should therefore apply heightened cardiovascular vigilance in postmenopausal women with MASLD, and consider whether standard risk algorithms adequately reflect their true cardiovascular burden.

8.4.3. Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS), affecting 5 – 15% of reproductive-age women, represents a high-risk intersection of hyperandrogenism, insulin resistance, and MASLD [167, 168]. MASLD prevalence in women with PCOS reaches 35 – 70%, substantially exceeding age- and BMI-matched controls, and fibrosis progression appears accelerated relative to MASLD patients without androgen excess [167]. The shared pathophysiological substrate of insulin resistance and chronic low-grade inflammation renders PCOS-associated MASLD a distinct clinical phenotype requiring integrated endocrine and hepatic surveillance alongside aggressive cardiometabolic risk management [171, 172].

8.4.4. Sex Differences in Fibrosis Progression and Cardiovascular Risk Amplification

While men demonstrate higher overall rates of fibrosis progression across the lifespan, postmenopausal women exhibit fibrosis progression rates that converge with or exceed those of men in

Table 1: Summary of Key Evidence Linking MASLD to Cardiovascular Outcomes

First Author, Year	Study Design	Population (N)	Outcome	Key Findings (Effect Estimate)	Adjustment Variables
Targher, 2016 [32]	Meta-analysis	34 studies N=164,494	CAD/Fatal CAD	OR 1.64 (95% CI 1.26-2.13) for prevalent CAD, HR 1.37 (1.10-1.72) for incident CAD	Age, sex, BMI, diabetes, hypertension, smoking, lipids (varied by study)
Wu, 2016 [76]	Meta-analysis	16 studies N=36,043	Myocardial Infarction	RR 1.64 (95% CI 1.30-2.08) for incident MI	Age, sex, BMI, diabetes, hypertension, smoking, dyslipidemia, and metabolic syndrome components
Targher, 2006 [57]	Meta-analysis	13 studies N=25,837	CV Mortality	OR 2.58 (95% CI 1.78-3.75) for CV death	Age, sex, diabetes, BMI, smoking, hypertension, lipids (varied by study)
Kim, 2018 [26]	Cohort study	N=4,731,801 Korean adults	CV Mortality	HR 1.04 (95% CI 1.00-1.08) for NAFLD vs no NAFLD after 10-year follow-up	Age, sex, smoking, alcohol, exercise, income, BMI, diabetes, hypertension, dyslipidemia, CKD
Mantovani, 2022 [86]	Meta-analysis	11 studies N=2,947,025	Heart Failure (any)	HR 1.50 (95% CI 1.33-1.70) for incident HF	Age, sex, BMI, diabetes, hypertension, smoking, dyslipidemia, CKD (varied by study)
Wijarnpreecha, 2017 [95]	Meta-analysis	5 studies N=320,906	HFpEF	OR 2.10 (95% CI 1.54-2.87) for HFpEF	Age, sex, BMI, diabetes, hypertension, CAD, smoking
Mantovani, 2018 [169]	Meta-analysis	7 studies N=183,419	Atrial Fibrillation	RR 1.23 (95% CI 1.10-1.38) for incident AF	Age, sex, BMI, diabetes, hypertension, smoking, alcohol, heart disease, CKD (varied by study)
Patel, 2016 [28]	Cross-sectional	N=290 patients	Carotid Plaque	OR 2.31 (95% CI 1.05-5.08) for carotid plaque in NASH vs simple steatosis	Age, sex, BMI, diabetes, hypertension, dyslipidemia, smoking
Simon, 2021 [68]	Cohort study	N=2,630 NAFLD patients	MACE	HR 1.69 (95% CI 1.04-2.75) for advanced fibrosis (F3-F4) vs F0-F2	Age, sex, race, BMI, diabetes, hypertension, dyslipidemia, smoking, prior CVD, statin use
Ekstedt, 2015 [66]	Cohort study	N=229 NAFLD patients 26-year follow-up	CV Mortality	HR 3.2 (95% CI 1.5-6.8) for NASH vs simple steatosis	Age, sex, BMI, diabetes, smoking
Mahfood Haddad, 2017 [99]	Meta-analysis	9 studies N=7,944,721	Stroke	OR 1.31 (95% CI 1.14-1.50) for ischemic stroke	Age, sex, smoking, BMI, diabetes, hypertension, dyslipidemia (varied by study)

Abbreviations: MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; CAD, coronary artery disease; MI, myocardial infarction; CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; AF, atrial fibrillation; CAC, coronary artery calcium; MACE, major adverse cardiovascular events; OR, odds ratio; HR, hazard ratio; RR, relative risk; CI, confidence interval; BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance.

Notes: Most studies were conducted during the NAFLD nomenclature era and are interpreted within the MASLD framework, given 99% diagnostic overlap. Substantial heterogeneity exists across studies in NAFLD/MASLD definition (imaging modality, biopsy criteria), follow-up duration, populations studied, and adjustment for confounders. Residual confounding by shared cardiometabolic risk factors (obesity, diabetes, hypertension, dyslipidemia) cannot be excluded despite multivariable adjustment. Effect estimates should be interpreted with consideration of these limitations.

certain cohorts, particularly in the presence of type 2 diabetes [169, 170, 177]. Advanced fibrosis in women carries cardiovascular risk amplification comparable to that observed in men, with hepatic fibrosis stage serving as an equally potent predictor of cardiovascular mortality irrespective of sex [66, 67]. However, the absolute cardiovascular event rates and the specific manifestations may differ: women with MASLD and advanced fibrosis demonstrate disproportionately elevated HFpEF risk and atrial fibrillation incidence relative to men, consistent with the broader sex-specific patterns of cardiovascular disease expression [83, 84, 91, 92]. A summary of the key evidence linking MASLD to cardiovascular outcomes is presented in **(Table 1)**.

8.4.5. Treatment Considerations

Sex-based differences in pharmacological response to MASLD therapies remain incompletely characterized but are clinically relevant. GLP-1 receptor agonists and SGLT2 inhibitors demonstrate broadly consistent hepatic and cardiovascular benefits across sexes in available trial data, though women were underrepresented in several landmark MASH trials, limiting sex-stratified conclusions [147, 149–151]. Pioglitazone carries particular caution in postmenopausal women given associations with accelerated bone density loss and increased fracture risk, warranting bone health assessment before initiation [152, 153]. Vitamin E supplementation in non-diabetic women with biopsy-proven MASH remains a guideline-supported option, though long-term safety data specific to postmenopausal women are limited [152, 153]. The potential role of menopausal hormone therapy (MHT) in modifying MASLD trajectory and cardiovascular risk in postmenopausal women is an area of active investigation; current evidence is insufficient to recommend MHT specifically for MASLD management, and decisions should be individualized based on established indications, contraindications, and cardiovascular risk profile [177, 179].

For internists, the key clinical takeaway is that sex and menopausal status should be integrated into MASLD risk stratification and management planning. Premenopausal women with MASLD warrant surveillance for accelerated risk transition at menopause; postmenopausal women require proactive cardiovascular risk reassessment; and women with PCOS should be systematically screened for MASLD regardless of BMI. A sex-informed approach to the liver-heart axis is not optional refinement – it is essential to delivering equitable, precision cardiometabolic care.

9. Limitations and Future Directions

Several limitations merit acknowledgment. First, the majority of outcome data cited in this review derive from studies conducted under NAFLD/NASH terminology. However, the 99% diagnostic overlap supports continuity of evidence; prospective validation of cardiovascular outcomes specifically under MASLD criteria remains limited. Second, substantial residual confounding by shared cardiometabolic risk factors – including obesity, type 2 diabetes, hypertension, and dyslipidemia – persists across observational studies linking MASLD to cardiovascular disease, and causality cannot be firmly established from available data. Third, diagnostic heterogeneity is considerable; studies vary widely in how hepatic steatosis was ascertained (ultrasound, MRI-PDFF, histology, or liver enzymes), how fibrosis was staged, and which cardiovascular endpoints were captured, limiting direct comparability across cohorts. Fourth, prospective data generated specifically within the MASLD nomenclature framework are scarce, and the anticipated benefits of the new terminology – including improved disease recognition, reduced stigma, and enhanced patient engagement – have not yet been validated in longitudinal studies.

Despite substantial progress in understanding the MASLD-cardiovascular axis, important knowledge gaps persist. These include elucidating the precise molecular mechanisms linking hepatic fibrosis to cardiovascular outcomes, developing integrated risk prediction models incorporating fibrosis stage alongside traditional cardiovascular risk factors, identifying therapies that simultaneously address hepatic and cardiovascular disease, characterizing ethnic and racial disparities in MASLD prevalence and treatment response, and conducting long-term studies assessing the real-world impact of nomenclature change on diagnosis rates and patient outcomes. Cost-effectiveness analyses of screening strategies and emerging pharmacotherapies also remain an important area for future investigation [180, 181].

10. Conclusion

The redefinition of fatty liver disease as MASLD represents more than nomenclature revision; it embodies a conceptual transformation recognizing the disease as a systemic metabolic disorder with significant cardiovascular implications. The liver-heart axis in MASLD is characterized by complex bidirectional interactions mediated by insulin resistance, chronic inflammation, oxidative stress, atherogenic dyslipidemia, and dysregulation of the gut-liver-heart axis. MASLD significantly increases risks of coronary artery disease, myocardial infarction, heart failure, particularly HFpEF, atrial fibrillation, stroke, and cardiovascular mortality, with hepatic fibrosis stage serving as a critical risk amplifier.

For internists managing patients across the cardiometabolic spectrum, the new MASLD nomenclature underscores the imperative for integrated care that addresses both hepatic and cardiovascular manifestations. Early identification through appropriate case-finding, accurate fibrosis assessment using non-invasive tools, comprehensive cardiovascular risk evaluation, and implementation of intensive lifestyle modifications form the foundation of management. Judicious use of cardiometabolic medications, including GLP-1 receptor agonists, SGLT2 inhibitors, statins, and antihypertensives, provides synergistic benefits for hepatic and cardiovascular health.

The transition to MASLD nomenclature is intended to facilitate better disease recognition, and may reduce stigmatization while aligning diagnostic criteria with pathophysiological understanding and therapeutic targets. As the field advances with emerging MASLD-specific pharmacotherapies and refined risk stratification tools, multidisciplinary collaboration will remain essential to optimize patient outcomes. Internists must embrace their central role in the comprehensive, integrated management of MASLD and its cardiovascular complications, recognizing that successful care requires addressing the liver-heart axis as an interconnected system rather than isolated organ dysfunction. Prospective validation of these anticipated benefits remains an important priority for future research.

Conflicts of Interest

All authors declare no conflicts of interest.

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Large Language Model

The authors declare that generative artificial intelligence (AI) tools, specifically Claude AI (Anthropic), were used solely to assist in grammar correction and paraphrasing during the preparation of this manuscript. No AI tool was used to generate ideas, analysis, or conclusions. All content was reviewed, verified, and approved by the authors, who take full responsibility for the integrity and accuracy of the manuscript.

Authors' Contributions

HAA contributed to the conceptualization of the study, literature search, data analysis, manuscript writing, and preparation of the original draft, while SAO contributed to manuscript review, critical revision, and editing.

Data Availability

No new data were generated or analyzed in this study. All supporting information is derived from previously published studies cited in the article.

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Case Series

Biopsy-Detected Microscopic Colitis and Nonspecific Chronic Inflammatory Change in Patients with Chronic Diarrhea and Normal Colonoscopy: A Two-Case Series

Jose Thomas[1,*], Nihal Ali[2], Aparna Gangoli[3], Apoorva Srijayadeva[2], Vijaya Kumar[2], Salfi P K[1]

1-Department of Emergency Medicine, Indiana Hospital and Heart Institute, Mangalore, Karnataka, India
2-Department of Gastroenterology, Indiana Hospital and Heart Institute, Mangalore, Karnataka, India
3-Department of Pathology, Indiana Hospital and Heart Institute, Mangalore, Karnataka, India

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ABSTRACT

Chronic diarrhea may occasionally persist despite macroscopically normal colonoscopy, and in selected patients, random colonic biopsy may reveal histologic abnormalities not apparent endoscopically. We report two illustrative cases of biopsy-detected microscopic or nonspecific inflammatory abnormalities in patients initially managed as having a functional bowel disorder. This retrospective descriptive case series included two adults identified during routine clinical practice over a recent two-year period (approximately 2024–2025) at a tertiary care hospital who underwent colonoscopy with random colonic biopsies despite macroscopically normal colonic mucosa, due to persistent diarrhea-predominant symptoms. Clinical follow-up was available for approximately six weeks in Case 1 and eight weeks in Case 2. In both patients, colonoscopy revealed macroscopically normal colonic mucosa, except for hemorrhoids. In Case 1, histopathology showed preserved crypt architecture, increased intraepithelial lymphocytes, and mild lamina propria inflammation, consistent with lymphocytic microscopic colitis. In Case 2, biopsy showed increased intraepithelial lymphocytes with chronic inflammatory infiltrates in the lamina propria, interpreted as nonspecific chronic inflammatory change. Both patients received colonic-release budesonide with short-term subjective symptomatic improvement on available follow-up. These cases illustrate that biopsy-detected microscopic or nonspecific inflammatory abnormalities may occasionally be identified in selected patients with persistent diarrhea and normal colonoscopy. They should not be interpreted as evidence of routine biopsy yield, but they support individualized biopsy decisions in carefully selected patients after exclusion of more common causes.

1. Introduction

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder characterized by recurrent abdominal symptoms associated with altered bowel habits in the absence of structural disease [1, 2]. In routine practice, however, patients initially labeled as having “IBS-like” symptoms may later prove to have an organic disorder, particularly when diarrhea-predominant symptoms persist despite empirical therapy [2, 3].

Microscopic colitis is a recognized cause of chronic watery diarrhea that often presents with normal or near-normal colonoscopic findings and requires histopathological confirmation [4, 5]. In contrast, nonspecific chronic inflammatory changes on random colonic biopsy are less diagnostically specific. They may reflect a range of processes, including post-infectious change, medication-related injury, resolving inflammation, or early/indeterminate inflammatory conditions. These entities should therefore not be interpreted as equivalent.

Current clinical practice supports selective rather than routine random colonic biopsy in patients with chronic watery diarrhea and normal endoscopy, particularly when symptoms are persistent, unexplained after basic evaluation, or refractory to standard therapy [6–9]. We present two illustrative cases in which a random colonic biopsy performed in the setting of persistent diarrhea and macroscopically normal colonoscopy demonstrated biopsy-based abnormalities that altered subsequent management.

2. Methods

This report is a retrospective descriptive case series of two adult patients evaluated in routine clinical practice at a tertiary care hospital. Cases were identified from endoscopy and pathology records over a recent two-year period (approximately January 2024 to December 2025) in which patients underwent colonoscopy with random colonic biopsies despite macroscopically normal colonic mucosa due to persistent diarrhea-predominant symptoms.

This manuscript is intended as an illustrative case series rather than an estimate of diagnostic yield. No denominator analysis was performed, and the report does not quantify the frequency with which random biopsies were negative during the study period.

Clinical data were obtained from chart review, including symptom duration, prior working diagnosis, colonoscopic findings,

* Corresponding author: Jose Thomas, Department of Emergency Medicine, Indiana Hospital and Heart Institute, Mangalore, Karnataka, India. Email: thomasjose265@gmail.com

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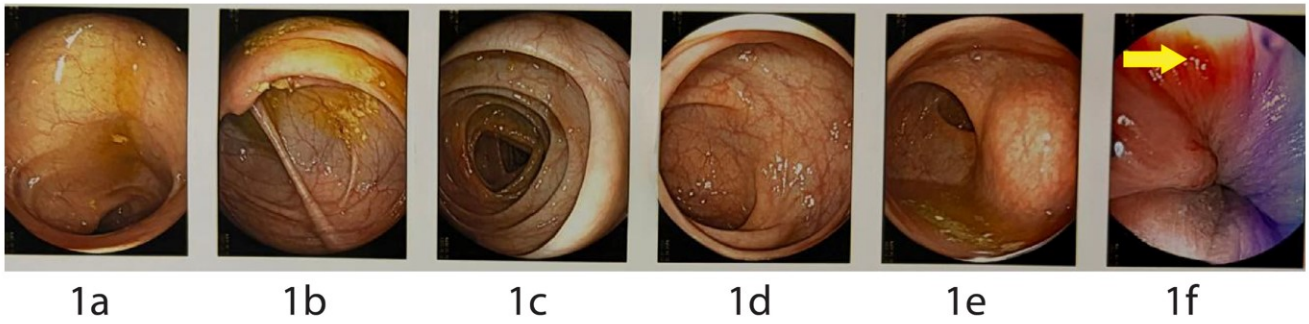

Figure 1: Colonoscopic images from Case 1 showing macroscopically normal colonic mucosa with hemorrhoids in the anal canal (yellow arrows).

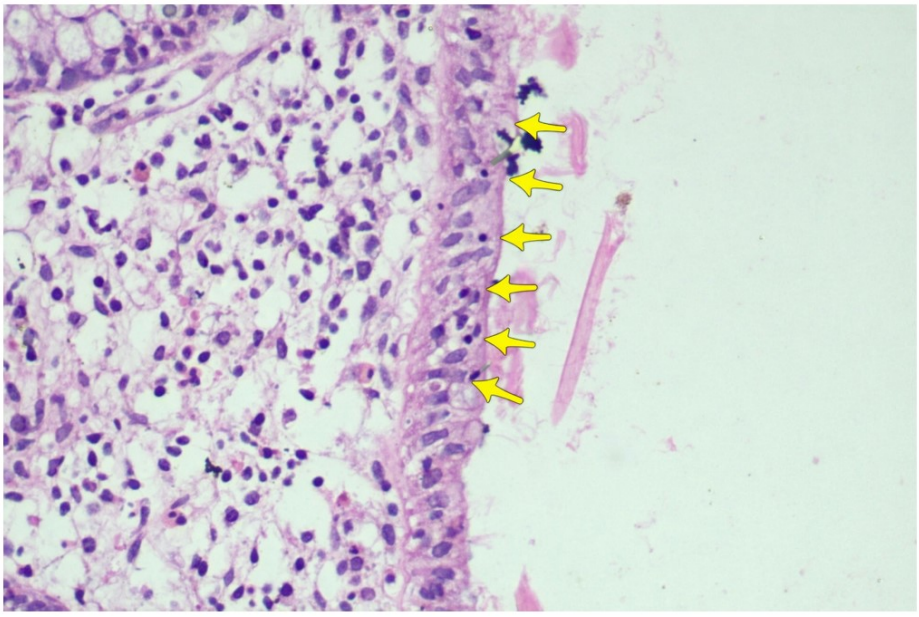

Figure 2: Histopathological section of colonic biopsy from Case 1 showing increased intraepithelial lymphocytes (yellow arrows) and mild lamina propria inflammation, consistent with lymphocytic microscopic colitis (H&E stain).

histopathology, treatment, and available follow-up. Written informed consent for publication of anonymized clinical details and images was obtained from both patients. This case series reflects routine clinical care and was not designed as an interventional study.

Random biopsies were obtained from macroscopically normal-appearing colonic mucosa at the treating gastroenterologist's discretion because of persistent symptoms despite prior symptomatic management. In both cases, biopsy samples were documented as having been taken from endoscopically normal colonic mucosa; however, the exact segmental distribution (including right-versus-left colonic sampling) and the exact number of biopsies were not consistently available in the archived procedural records. Accordingly, this report should not be interpreted as reflecting a standardized or reproducible biopsy protocol. Histopathological interpretation was based on routine pathology reporting. In Case 1, the biopsy findings were considered consistent with lymphocytic microscopic colitis. In Case 2, the findings were interpreted more cautiously as nonspecific chronic inflammatory change rather than a definitive, discrete inflammatory colitis syndrome.

Alternative causes of chronic diarrhea were assessed clinically before colonoscopy, including symptom review, medication history, routine laboratory evaluation, and endoscopic exclusion of gross structural pathology. However, the retrospective nature of this report limits the completeness of uniform documentation for stool testing, celiac serology, and other secondary-cause exclusion across both cases, and this is acknowledged as a limitation.

3. Case Series

3.1. Case 1

A 43-year-old woman presented with a six-month history of chronic loose stools with increased stool frequency and intermittent abdominal discomfort. She had previously been managed symptomatically for a functional bowel disorder without sustained improvement. There was no history of gastrointestinal bleeding, clinically significant weight loss, nocturnal diarrhea, or family history of inflammatory bowel disease. The available chart review documented basic laboratory assessment, including routine hemogram and biochemical evaluation, without evidence of overt systemic inflammatory or metabolic disease. Medication review did not identify a clearly

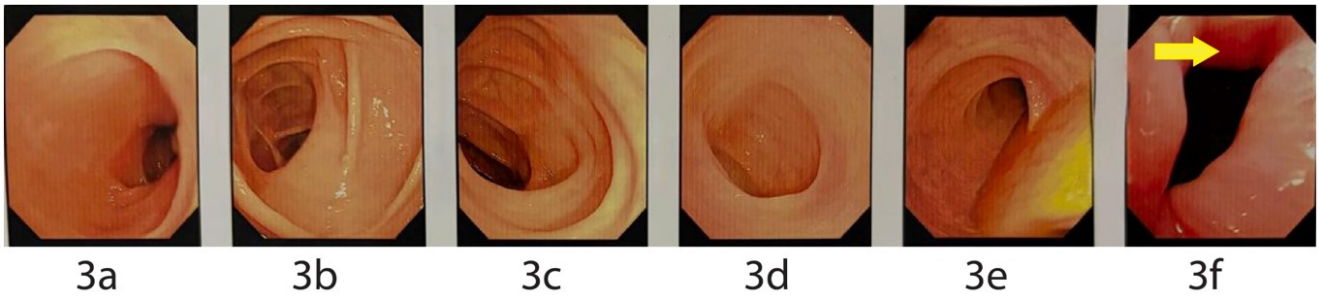

Figure 3: Colonoscopic images from Case 2 demonstrating macroscopically normal colonic mucosa with hemorrhoids in the anal canal (yellow arrows).

documented precipitating drug exposure. Stool studies and celiac serology were not uniformly documented in the retrospective record; therefore, complete standardized exclusion of all secondary causes cannot be confirmed.

Because of persistent diarrhea-predominant symptoms despite prior empirical treatment, colonoscopy was performed. This demonstrated hemorrhoids with otherwise macroscopically normal colonic mucosa **(Figure 1)**. Random biopsies were obtained from normal-appearing colonic mucosa, but the exact segmental biopsy distribution and number of fragments were not consistently available in the archived endoscopy record.

Histopathological examination showed preserved crypt architecture with a focal increase in intraepithelial lymphocytes and mild lamina propria inflammation **(Figure 2)**. In the clinical and histologic context, this was interpreted as consistent with lymphocytic microscopic colitis [4, 5]. The patient was treated with colonic-release budesonide. Available follow-up documentation reflected short-term symptomatic improvement over approximately six weeks. Longer-term relapse status after tapering was not uniformly available in the archived record. No repeat histology or objective inflammatory biomarker reassessment was performed.

3.2. Case 2

A 37-year-old man presented with approximately 1.5 years of chronic loose stools associated with bloating. He had previously been labeled as having IBS and treated symptomatically without meaningful improvement. There was no history of overt gastrointestinal bleeding, major weight loss, or nocturnal symptoms documented in the available records. The available chart review documented a basic laboratory assessment without clear abnormality, and the medication review did not identify a clearly documented high-risk exposure. However, stool studies, celiac serology, and complete standardized secondary-cause evaluation were not uniformly documented in the retrospective record and, therefore, cannot be considered comprehensively excluded.

Because of persistent diarrhea despite prior symptomatic therapy, a colonoscopy was performed. The colonic mucosa appeared macroscopically normal except for hemorrhoids **(Figure 3)**. Random colonic biopsies were obtained from normal-appearing mucosa, but exact segmental biopsy distribution and biopsy counts were not uniformly available in the archived record.

Histopathology demonstrated increased intraepithelial lymphocytes with chronic inflammatory infiltrates in the lamina propria **(Figure 4)**. Unlike Case 1, these findings were considered less specific and were interpreted more cautiously as nonspecific chronic inflammatory change rather than a definitive microscopic colitis subtype. Given the persistent symptoms, absence of gross endoscopic disease, and biopsy-based inflammatory changes, a therapeutic trial of colonic-release budesonide was undertaken after clinical correlation. The available follow-up documentation reflected short-term subjective improvement over approximately eight weeks after initiation of budesonide. However, the retrospective record did not clearly document a complete tapering schedule, longer-term relapse status, or repeat objective reassessment. Therefore, longer-term diagnostic stability for Case 2 remains uncertain.

4. Discussion

This report describes two illustrative cases in which random colonic biopsy obtained during macroscopically normal colonoscopy demonstrated histologic abnormalities in patients with persistent diarrhea-predominant symptoms initially managed as functional bowel disorder. Importantly, this case series should not be interpreted as evidence of diagnostic yield or broad “diagnostic utility,” because only two positive cases are presented, and no denominator is provided for the number of patients with normal colonoscopy who underwent biopsy during the same period.

The first case is the more diagnostically robust of the two. The histologic finding of increased intraepithelial lymphocytes with preserved crypt architecture and mild lamina propria inflammation is compatible with lymphocytic microscopic colitis in the appropriate clinical setting [4, 5]. Microscopic colitis is a well-recognized cause of chronic watery diarrhea with normal or near-normal endoscopic appearance, and selective biopsy is appropriate when diarrhea is persistent, unexplained, and disproportionate to a purely functional diagnosis [6–9].

The second case requires greater caution. The label of nonspecific chronic inflammatory change does not by itself establish a discrete inflammatory colitis syndrome. Such changes may be seen in a range of contexts, including post-infectious change, medication-related injury, early or indeterminate inflammatory disease, or nonspecific reactive inflammation. Accordingly, this case should be viewed as an example of biopsy-detected nonspecific inflammatory abnormality rather than definitive proof of a well-defined inflammatory colitis entity.

The short-term symptomatic improvement observed after budesonide in both patients should also be interpreted cautiously. A therapeutic response, especially in a patient with less specific histology, should not be regarded as diagnostic confirmation. In the second case in particular, budesonide was used as a clinically reasoned therapeutic trial in the setting of persistent symptoms and biopsy-based inflammatory change. Still, the response does not establish etiologic certainty.

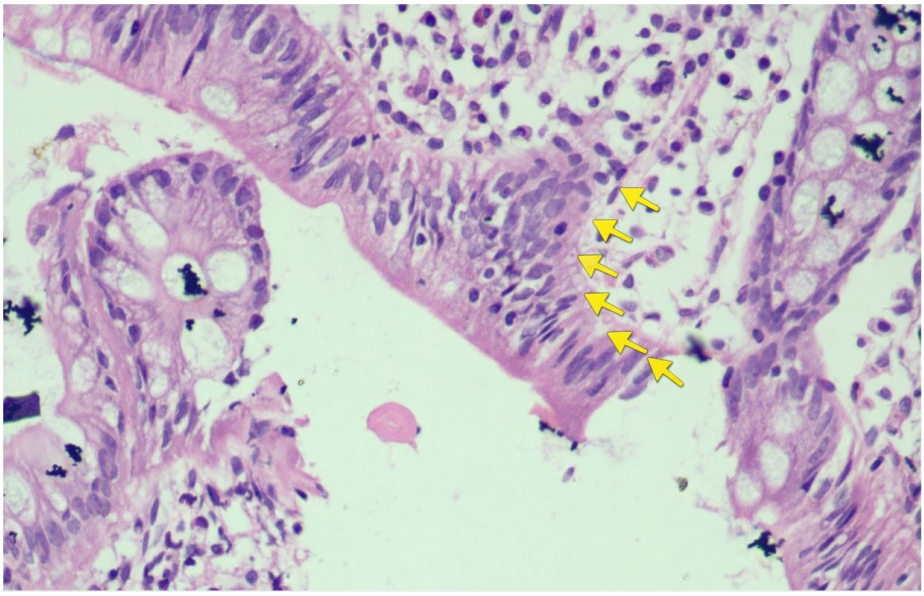

Figure 4: Hematoxylin and eosin-stained colonic biopsy from Case 2 showing increased intraepithelial lymphocytes (yellow arrows) and chronic inflammatory infiltrates within the lamina propria, interpreted more cautiously as nonspecific chronic inflammatory change rather than a definitive microscopic colitis subtype. (Original pathology report basis; exact magnification not available from archived image.)

Recent guideline-based literature supports a selective rather than indiscriminate biopsy approach in patients with chronic watery diarrhea and normal endoscopy, particularly when symptoms are persistent, unexplained, or clinically discordant with a straightforward functional diagnosis [6–9]. Contemporary guidance emphasizes histologic confirmation for microscopic colitis while recognizing that diagnostic yield is influenced by pretest probability and biopsy adequacy [6].

Both patients in this series represented comparatively low-pretest-probability presentations for biopsy-detected microscopic or inflammatory abnormalities because they were younger than the typical demographic in whom microscopic colitis is classically emphasized and lacked strongly suggestive alarm features. This lower pretest probability is important when interpreting the manuscript, because it limits generalizability and reinforces that biopsy in these cases reflected individualized clinical judgment in the setting of persistent, treatment-refractory diarrhea rather than a broadly applicable rule.

These cases support a selective, individualized approach rather than routine random biopsy in all patients with IBS-like symptoms. Biopsy is more defensible in patients with persistent diarrhea-predominant symptoms, chronic watery stools, failure of standard symptomatic therapy, or clinical concern that exceeds the pretest probability of a purely functional disorder. Conversely, indiscriminate biopsy in all patients with a normal colonoscopy may increase costs, yield nonspecific histologic findings, and risk over-interpretation without necessarily improving management.

5. Limitations

This report has several important limitations. First, it is a two-patient retrospective case series and is inherently hypothesis-generating rather than practice-defining. Second, no sampling denominator is provided, so the biopsy yield cannot be estimated. Third, the workup for secondary causes of chronic diarrhea was not uniformly documented in a protocolized manner across both patients because of retrospective data capture. Fourth, biopsy protocol details, including exact segmental sampling and standardized histologic thresholds, were not completely available in the chart for both cases. Fifth, pathology was interpreted in routine clinical practice, and the manuscript does not include formal blinded re-review by a gastrointestinal pathologist. Finally, clinical improvement was assessed by short-term subjective symptom follow-up rather than standardized outcome metrics, biomarker reassessment, or long-term relapse documentation.

Overall, the present report is best understood as a small illustrative case series demonstrating that biopsy-detected microscopic or nonspecific inflammatory abnormalities may occasionally be encountered in selected patients with persistent diarrhea and normal colonoscopy. It should not be used to justify routine biopsy in all patients with generic IBS-like presentations.

6. Conclusion

This two-case series illustrates that biopsy-detected microscopic or nonspecific inflammatory abnormalities may occasionally be identified in carefully selected patients with persistent diarrhea-predominant symptoms despite macroscopically normal colonoscopy. These observations should not be interpreted as evidence of routine diagnostic yield or broad practice-changing utility. Rather, they support a selective, individualized decision to obtain random colonic biopsies in patients whose clinical presentation remains atypical for uncomplicated functional bowel disorder after appropriate evaluation.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Informed Consent

Written informed consent for publication of anonymized clinical details and images was obtained from both patients.

Large Language Model

The authors used ChatGPT (OpenAI: GPT-5 series) for language editing, grammar refinement, and formatting assistance during manuscript preparation. The authors independently reviewed, verified, and approved all scientific content and take full responsibility for the accuracy and integrity of the manuscript.

Author Contributions

JT handled conceptualization, data curation, investigation, literature review, drafting the manuscript, review and editing, and coordination of the submission. NA supervised the work, managed the patient, performed the endoscopic evaluation, and contributed to writing, review, and editing. AG carried out histopathological interpretation, validation, and contributed to writing, review, and editing. AS contributed to clinical review, supervision, and writing, review, and editing. VK provided clinical oversight, contributed to writing, review, and editing, and gave final approval. SPK provided clinical oversight, contributed to writing, review, and editing, and gave final approval. All authors approved the final manuscript.

Data Availability

All relevant clinical information supporting the findings of this report is included within the manuscript. Additional de-identified details may be available from the corresponding author on reasonable request, subject to patient confidentiality.

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