NTTデータ数理システム学生研究奨励賞

フィブラート系薬剤と胆道系有害事象の不均衡解析 ～JADERおよびFAERSデータベースを用いた評価～

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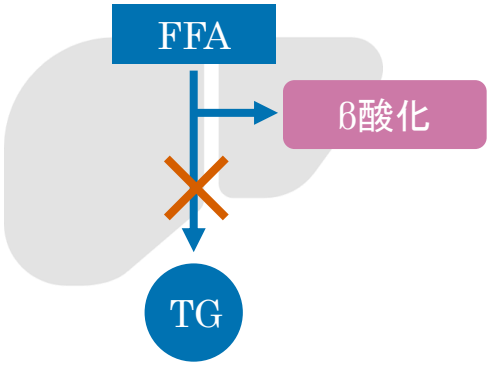
背景：フィブラート系薬剤について

フィブラート系薬剤について

- PPARα作動薬として、脂質異常症の治療薬に広く用いられている
- 現在日本で主に使われているのは、ベザフィブラート、フェノフィブラート、ペマフィブラートの3種

〈詳しい作用機序〉



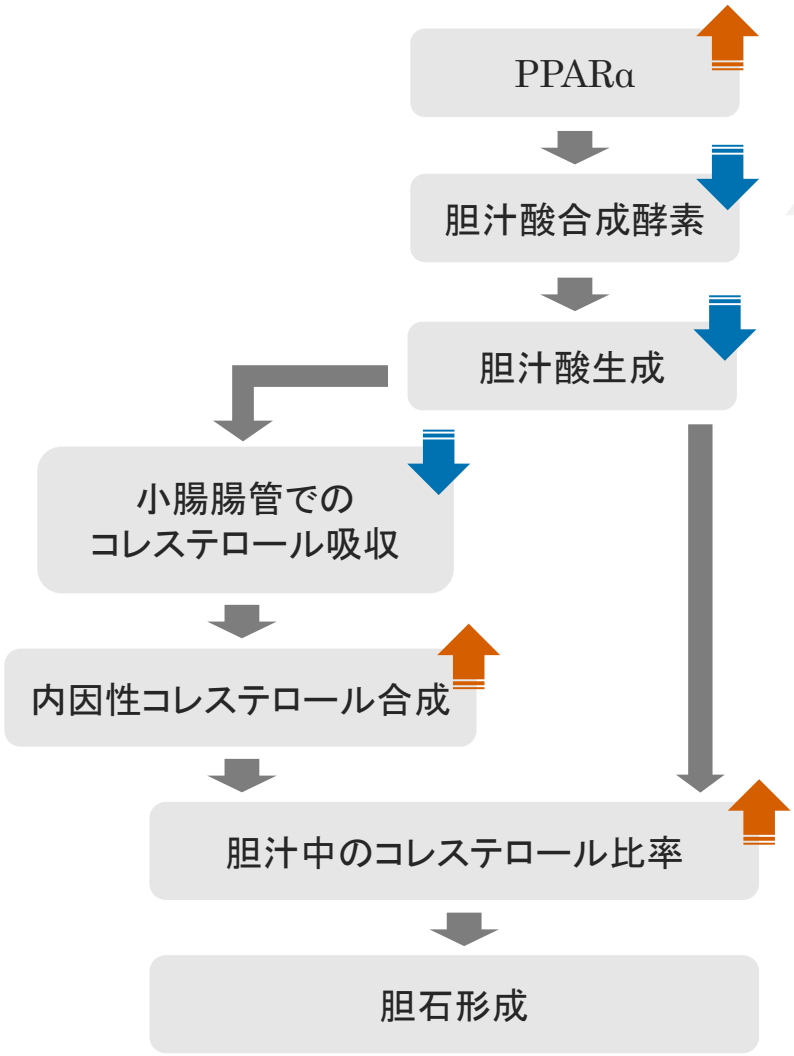
- ✓ 肝臓で脂肪酸のβ酸化を亢進し、TGの合成を抑えることにより、VLDL産生を抑制する[1]
- ✓ LPLやHLを増加・活性化し、リポ蛋白内のTG分解を促進する[1]
- ✓ ApoA-Ⅰ やABCA1の合成を促進することにより、血中HDLを増加させる[1]

表1 フィブラート系薬剤の作用機序[2,3]

	PPARα活性化	PPARγ活性化	備考
ベザフィブラート	強い	中程度	PPARαとPPARγのデュアルアゴニスト
フェノフィブラート	非常に強い	弱い	PPARα選択性が高い
ペマフィブラート	非常に強い	極めて弱い	選択的PPARαモジュレーター（SPPARMα）であり、副作用が少ない

背景：フィブラート系薬剤と胆道系有害事象

- フィブラート系薬剤は高脂血症治療薬として有益な一方で、胆石症や胆嚢炎を中心とした胆道系有害事象が示唆されている



PPARαが胆汁酸合成律速酵素であるCYP7A1とCYP27A1の活性を抑制することで胆汁酸産生が低下する[4]

- ペマフィブラートの52週間第Ⅲ相試験では、胆石症の発現率が5.3%と報告された[5]
- フィブラート系薬剤使用と胆石症との関連を示唆する症例集積報告も存在[6]
- 左図のように、作用機序的側面からもフィブラート系薬剤と胆道系有害事象には関連がある可能性が懸念されている

フィブラート系薬剤は胆石症や胆嚢疾患のある患者へ禁忌であり、有害事象が起こると治療継続が困難[5]

背景：フィブラート系薬剤の胆道系有害事象に関する現段階の課題

現段階で作用機序的側面や臨床試験などの複数の研究において胆道系有害事象の可能性が指摘されているが、課題も存在する

現段階の課題

- 臨床試験は管理された条件下で実施されるため、必ずしも日常診療を反映しない可能性[7,8]
- ペマフィブラートの使用は日本、シンガポール、タイなど一部の国に限られており、有害事象に関するデータが不足[9]

SRSの活用

- 臨床現場から広く有害事象報告を収集する性質上、日常診療を反映しやすい[10,11]
- 新薬や使用地域が限られている薬剤に関して、補完的な情報を提供できる

臨床試験に加えて複数のデータソースを解析し、
それらの結果を統合して判断することが重要[12]

目的

本研究の目的

自発報告システム（SRS）データベースを用いて、
フィブラート系薬剤と胆道系有害事象との関連を評価する

1. フィブラート間でのシグナル頑健性の違いを確認する
   - 3種のフィブラート系薬剤（ペマフィブラート、フェノフィブラート、ベザフィブラート）間で報告傾向の違いはあるか？
2. 報告時期の傾向を分析し、推奨されるモニタリング時期を特定する
   - 投与初期に有害事象報告が集中しているか？それとも投与継続に伴い有害事象報告が増加するのか？

今後のさらなる研究の推進に向けた問題提起を行い、
薬剤による有害事象発現の予防に寄与する

治療継続や
患者のQOL向上
へ寄与

有害事象発現に
伴う手術などの
負担を削減

患者さんがより良い医療を受けるために、
副作用モニタリングは非常に重要である

方法：実験環境

表2　実験環境

OS	Windows 11 Pro
CPU	12th Gen Intel (R) Core (TM) i7-12700T
メモリ	16.0 GB
ソフトウェア	MSIP ver. 1.10.1 Python ver.3.13

※ 基本的なデータ結合、集計、クリーニング作業をMSIP上で実施。最後のシグナル指標算出および図表作成には、MSIP上でPythonを使用

使用データベース

独立行政法人 医薬品医療機器総合機構（PMDA）が提供するJADERおよびアメリカ食品医薬品局（FDA）が提供するFAERSの2つの医薬品副作用データベースを用いた。

JADER：2004/4~2025/5までを使用（https://www.pmda.go.jp/safety/info-services/drugs/adr-info/suspected-adr/0003.html）

FAERS：2014Q1~2024Q4までを使用（https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html）

JADER: the Japanese Adverse Drug–Event Report
FAERS: the U.S. Food and Drug Administration Adverse Event Reporting System

方法：MSIPを用いる利点

- ノーコードでワークフローを構築できる
  - 2×2分割表における基本的な数え上げ作業、データベース内の情報のクリーニング作業がノーコード、直感的な操作で行えることから、薬学部というプログラミング技術を専門的に学ばない学部の学生でも、簡単に解析を実施することができる
  - 専門的な解析が必要になった場合でも、AlkanoやText Mining Studioなどの拡張ツールやPythonノードの追加によって行うことができ、応用性が高い。特に、医薬品副作用データベースでは自由記述の項目が含まれるため、解析にあたって用語の抽出等をMSIP上で簡単に行うことができる

- 再現性が高い
  - 分析手順を保存・共有することができ、ノード単位で何を行ったかを追うことができるため、解析結果の再現性が高い

- サポートの手厚さ
  - チュートリアルや攻略ガイド、ムービーなどの公式教材が整備されており、Pythonスキルの有無に依存せず、チーム全体での作業が可能

プログラミングを専門とする研究者による活用だけでなく、プログラミングを専門としない研究者でもデータ解析を簡単に行うことができる

方法：データセット作成

JADER：DRUG/HIST を DEMO に左外部結合して患者単位の報告（ICSR）とした
FAERS：DEMOの最大versionを採用し重複除去→DRUG左外部結合/OUTC・THER左外部結合し患者単位の報告とした

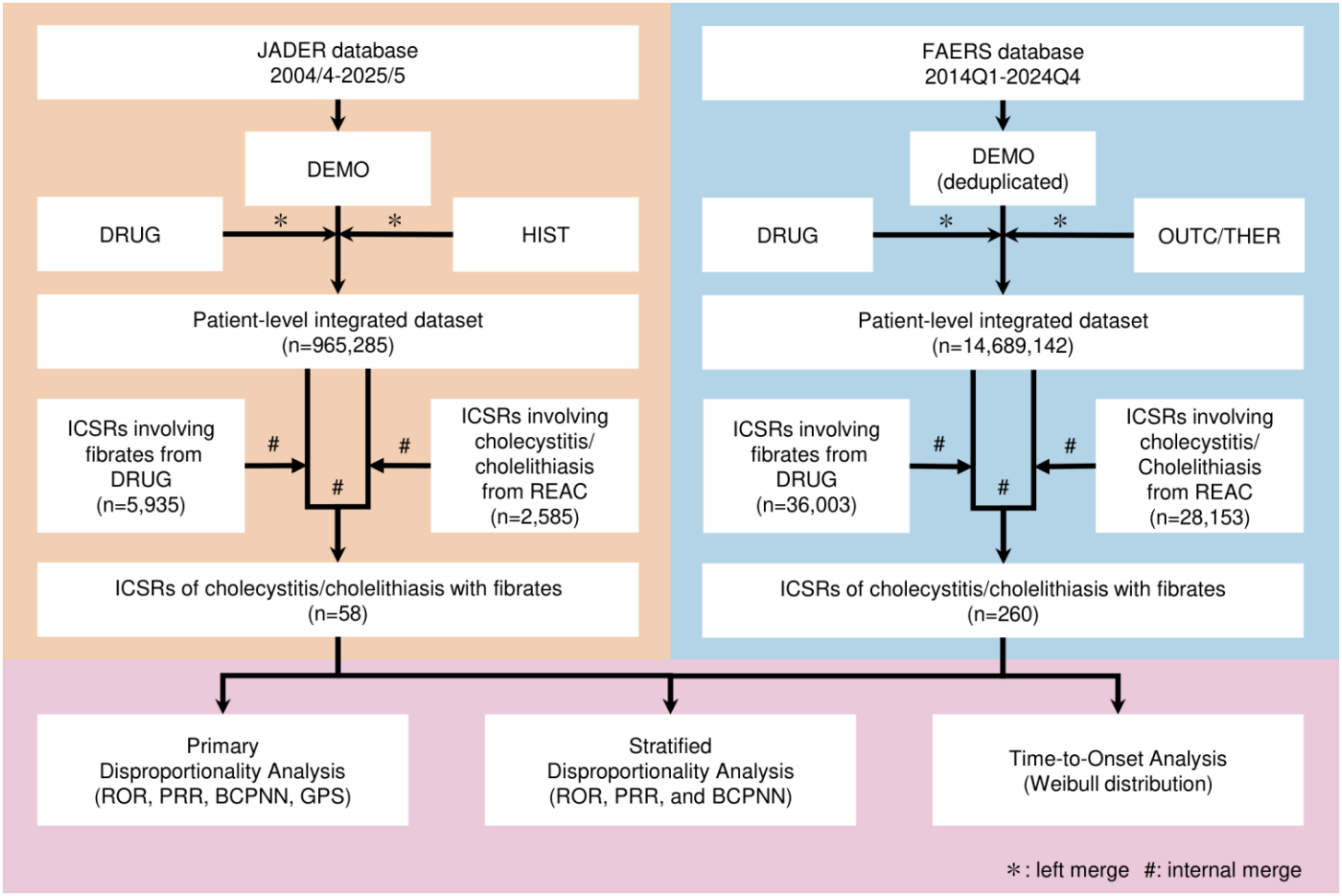
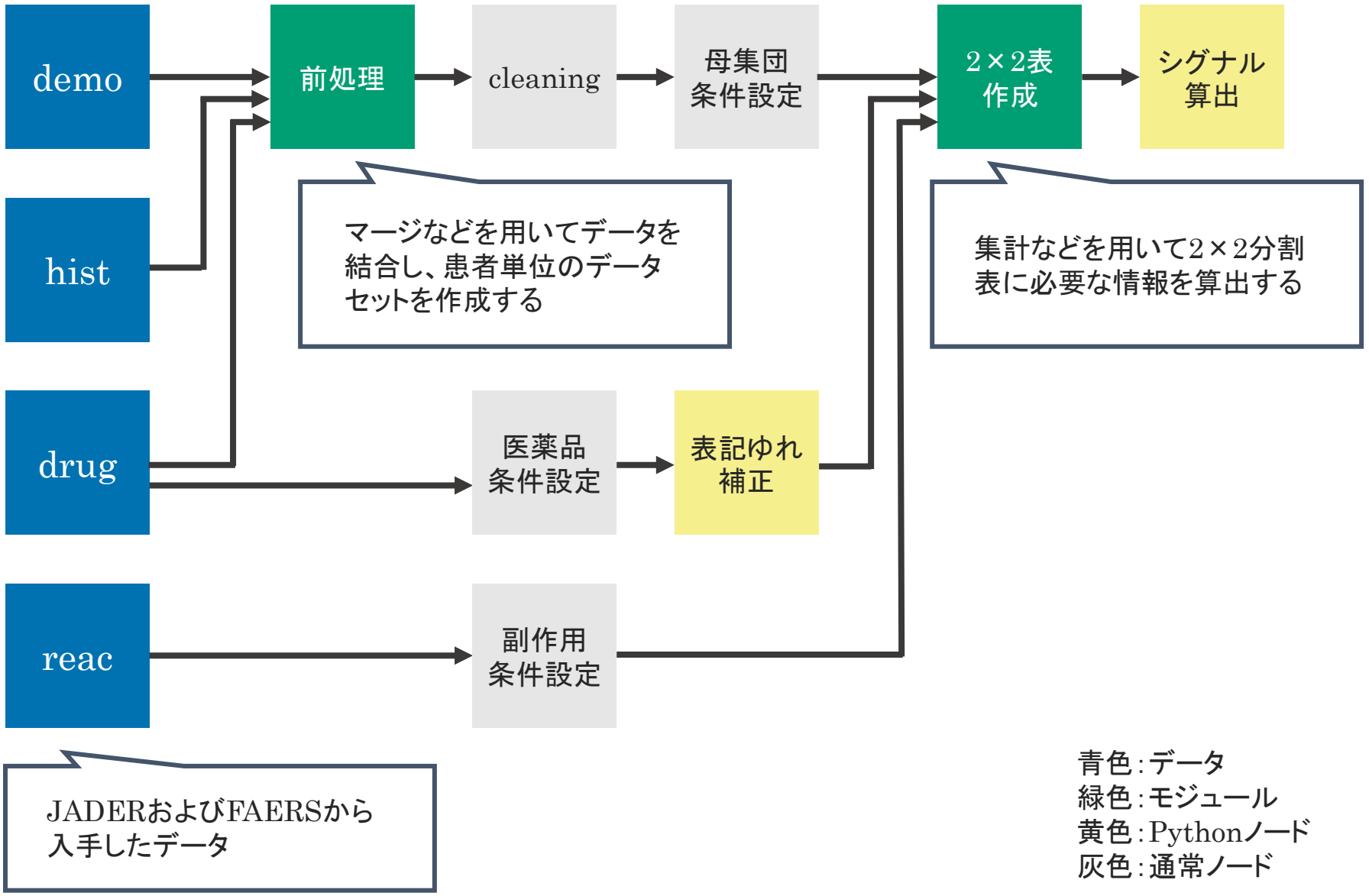


図1 データベースの統合方法

方法：MSIPにおけるワークフロー作成



方法：医薬品条件および副作用条件

医薬品条件

〈JADER〉
医薬品（一般名）列において「ペマフィブラート」、「フェノフィブラート」、「ベザフィブラート」の3つを選択

〈FAERS〉
“PEMAFIBRATE” “FENOFIBRATE” “FENOFIBRIC ACID” “CHOLINE FENOFIBRATE” “BEZAFIBRATE” を検索し、Fenofibrate の綴りゆれを標準化

副作用条件

- MedDRA/J ver.28.0を使用
- HLT「胆嚢炎および胆石症/Cholecystitis and cholelithiasis」以下の14つのPTを胆道系有害事象として抽出

MedDRA/J 検索ツール：
https://www.jmo.gr.jp/jmo/servlet/mdrLoginTop

表3 PT一覧

PT Code	Preferred Term
10008612	胆嚢炎/Cholecystitis
10008614	急性胆嚢炎/Cholecystitis acute
10008617	慢性胆嚢炎/Cholecystitis chronic
10008629	胆石症/Cholelithiasis
10008630	閉塞性胆石症/Cholelithiasis obstructive
10017649	胆石性イレウス/Gallstone ileus
10056668	気腫性胆嚢炎/Emphysematous cholecystitis
10062631	感染性胆嚢炎/Cholecystitis infective
10066884	偽胆石症/Pseudocholelithiasis
10068884	脱落胆石/Cholelithiasis migration
10082088	出血性胆嚢炎/Haemorrhagic cholecystitis
10084002	虚血性胆嚢炎/Ischaemic cholecystitis
10088969	好酸球性胆嚢炎/Eosinophilic cholecystitis
10090325	急性壊死性胆嚢炎/Acute cholecystitis necrotic

方法：各シグナル指標について

ROR

1. n11≥3
2. ROR025（信頼区間下限値）>1
3. P value<0.05

- ✓ JADERで標準的に用いられているシグナル指標[13]
- ✓ 感度が高く、その分偽陽性も出やすい[14]

$$ROR = \frac{n_{11}/n_{21}}{n_{12}/n_{22}} \qquad 95\%CI = \exp\left\{\log(ROR) \pm 1.96\sqrt{\frac{1}{n_{11}} + \frac{1}{n_{12}} + \frac{1}{n_{21}} + \frac{1}{n_{22}}}\right\}$$

PRR

1. n11≥3
2. PRR025（信頼区間下限値）>2
3. χ^2>4

※ RORで広くスクリーニングし、PRRでより厳格に評価するという観点から、今回はPRR信頼区間下限値>2の基準を採用

- ✓ 英国MHRAにおいて用いられているシグナル指標[14]
- ✓ 特定薬剤における特定有害事象の報告割合を、他の全ての薬剤における同事象の報告割合と比較する[15]

$$PRR = \frac{n_{11}/n_{1+}}{n_{21}/n_{2+}} \qquad 95\%CI = \exp\left\{\log(PRR) \pm 1.96\sqrt{\frac{1}{n_{11}} - \frac{1}{n_{1+}} + \frac{1}{n_{21}} - \frac{1}{n_{2+}}}\right\}$$

方法：各シグナル指標について

IC（BCPNN）

1. IC025（信頼区間下限値）>0

- ✓ WHOのデータベースVigiBaseにおいて採用されているベイズ的シグナル検出手法[16]
- ✓ RORやPRRと比較してn数が小さい場合の偽陽性が出にくい

EBGM（GPS）

1. EBGM05（信頼区間下限値）>2

- ✓ FDAで用いられているシグナル指標[17]
- ✓ 層別化による交絡調整が可能であるという利点がある[18]

頻度論（ROR, PRR）

- 計算で簡便に求められる
- N数が少ない場合に偽陽性となりやすい

ベイズ論（IC, EBGM）

- N数が少なくても頑健な結果が得られやすい
- 計算が煩雑かつ、事前分布の影響を受けるため、適切に設定する必要がある

➢ **複数のシグナル指標**を用いて総合的に評価する必要がある

方法：Weibull解析について

- Weibull分布とは
  - 機械が故障するまでの期間や生物の寿命などを分析するのに多く用いられる確率分布

βの時、確率密度分布は以下の式で表される[19]

$$p(x|\beta,\alpha) = \frac{\beta}{\alpha} \cdot \left(\frac{x}{\alpha}\right)^{\beta-1} \cdot exp\left(-\left(\frac{x}{\alpha}\right)^{\beta}\right), x > 0$$

形状パラメータβおよび尺度パラメータαは、下記の対数尤度関数を最大化することによって推定[19]

$$\log L(\beta,\alpha) = n\log\beta - n\beta\log\alpha + (\beta-1)\sum_{i=1}^{n}\log x_i - \sum_{i=1}^{n}(\frac{x_i}{\alpha})^{\beta}$$

βおよびαの信頼区間に関しては、今回n数が少ないことからブートストラップ法にて算出[20]

形状パラメータβの解釈

β<1：初期故障型----------薬物投与初期に有害事象報告が集中している
β=1：偶発故障型----------投与後のどの時点でも、有害事象報告頻度が一定
β>1：遅発故障型----------薬物投与から時間が経つほど有害事象報告が増加する

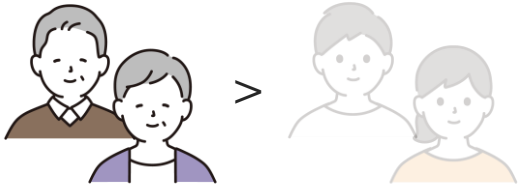
結果：報告の基本的傾向

表4 JADERにおける報告の基本的傾向

Variables	Pemafibrate	Fenofibrate	Bezafibrate
Sex			
Male	19 [67.9]	14 [70.0]	9 [69.2]
Female	9 [32.1]	6 [30.0]	4 [30.8]
Not Specified	0 [0.0]	0 [0.0]	0 [0.0]
Age			
20–50 years	9 [32.1]	4 [20.0]	5 [38.5]
≥60 years	19 [67.9]	16 [80.0]	8 [61.5]
Reporter			
Healthcare Professional	28 [100.0]	19 [95.0]	13 [100.0]
Consumer	0 [0.0]	1 [5.0]	0 [0.0]
Unknown	0 [0.0]	0 [0.0]	0 [0.0]

男女別の報告傾向

年齢別の報告傾向



- 男性の方が女性よりも相対的に報告が多かった
- 60歳代以上の方が、20-50歳代よりも相対的に報告が多かった
- ペマフィブラートについても継続的に報告されている

結果：主解析

JADER

Drug	N	ROR (95% CI)	P value	PRR025	χ^2	IC025	EBGM05	Forest plot of ROR	ROR	PRR	IC	EBGM
Pemafibrate	28	16.99 (11.61–24.86)	<0.001	11.32	398.86	2.85	11.35		✓	✓	✓	✓
Fenofibrate	20	3.53 (2.27–5.49)	<0.001	2.26	35.61	1.00	2.49		✓	✓	✓	✓
Bezafibrate	13	1.51 (0.88–2.61)	0.17	0.88	2.24	-0.24	1.21					
Overall	58	3.74 (2.88–4.85)	<0.001	2.86	112.54	1.42	2.92		✓	✓	✓	✓

FAERS

Drug	N	ROR (95% CI)	P value	PRR025	χ^2	IC025	EBGM05	Forest plot of ROR	ROR	PRR	IC	EBGM
Pemafibrate	3	6.40 (2.05–19.99)	<0.05	2.06	13.51	-0.02			✓	✓		
Fenofibrate	233	3.65 (3.21–4.15)	<0.001	3.19	441.11	1.65			✓	✓	✓	
Bezafibrate	25	6.24 (4.21–9.26)	<0.001	4.19	108.68	1.80			✓	✓	✓	
Overall	260	3.81 (3.37–4.31)	<0.001	3.36	530.99	1.72			✓	✓	✓	

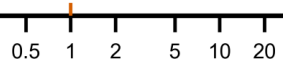


図2 JADER, FAERSにおける主解析結果

※1つのICSRに複数のフィブラートを含み得るため薬剤別件数は相互排他的ではない（Drug-event pairs）

- ペマフィブラートとフェノフィブラートではROR, PRR, IC, EBGMの全指標が統計学的に有意であった
- ベザフィブラートでは有意なシグナルは認められなかった

結果：層別解析

Pemafibrate

JADER

Subgroup	N	ROR (95% CI)	P value	PRR025	χ^2	IC025	Forest plot of ROR	ROR	PRR	IC
Male	19	15.79 (9.94–25.08)	<0.001	9.73	248.42	2.47		✓	✓	✓
Female	9	18.05 (9.23–35.30)	<0.001	9.10	137.35	1.77		✓	✓	✓
≥60 years	19	14.53 (9.16–23.07)	<0.001	8.96	226.60	2.41		✓	✓	✓
20-50 years	9	23.79 (12.11–46.71)	<0.001	11.93	183.98	1.89		✓	✓	✓
BMI≥25	4	8.11 (2.97–22.12)	<0.05	2.98	23.79	0.39		✓	✓	✓
BMI<25	8	13.83 (6.80–28.12)	<0.001	6.74	90.64	1.50		✓	✓	✓
Overall	28	16.99 (11.61–24.86)	<0.001	11.32	398.86	2.85		✓	✓	✓

Fenofibrate

JADER

Subgroup	N	ROR (95% CI)	P value	PRR025	χ^2	IC025	Forest plot of ROR	ROR	PRR	IC
Male	14	3.74 (2.20–6.34)	<0.001	2.20	27.47	0.89		✓	✓	✓
Female	6	2.89 (1.29–6.46)	<0.05	1.29	7.31	0.08		✓		✓
≥60 years	16	3.61 (2.20–5.93)	<0.001	2.20	29.64	0.92		✓	✓	✓
20-50 years	4	2.91 (1.09–7.81)	0.05	1.09	4.95	-0.24				
BMI≥25	4	2.41 (0.89–6.51)	0.09	0.90	3.21	-0.42				
BMI<25	5	2.40 (0.99–5.79)	0.06	0.99	4.01	-0.24				
Overall	20	3.53 (2.27–5.49)	<0.001	2.26	35.61	1.00		✓	✓	✓

Bezafibrate

JADER

Subgroup	N	ROR (95% CI)	P value	PRR025	χ^2	IC025	Forest plot of ROR	ROR	PRR	IC
Male	9	1.58 (0.82–3.04)	0.20	0.82	1.88	-0.35				
Female	4	1.28 (0.48–3.41)	0.56	0.48	0.24	-1.02				
≥60 years	8	1.18 (0.59–2.37)	0.56	0.59	0.22	-0.76				
20-50 years	5	2.39 (0.99–5.79)	0.06	0.99	4.00	-0.24				
BMI≥25	6	2.38 (1.05–5.38)	<0.05	1.05	4.62	-0.15		✓		
BMI<25	5	1.48 (0.61–3.58)	0.40	0.62	0.78	-0.74				
Overall	13	1.51 (0.88–2.61)	0.17	0.88	2.24	-0.24				

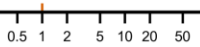


図3 JADER, FAERSにおける層別解析結果

全てのサブグループでシグナルが認められた

- ペマフィブラートでは性別・年齢・BMIのすべての層でROR・PRR・ICの有意なシグナルが検出された
- フェノフィブラートでは男性・女性・年齢≥60歳代の層でRORとICが有意、PRRは男性と年齢≥60歳代の層のみ有意
- ベザフィブラートはBMI≥25の層でのみRORが有意

結果：Time-to-onset解析（Weibull解析）

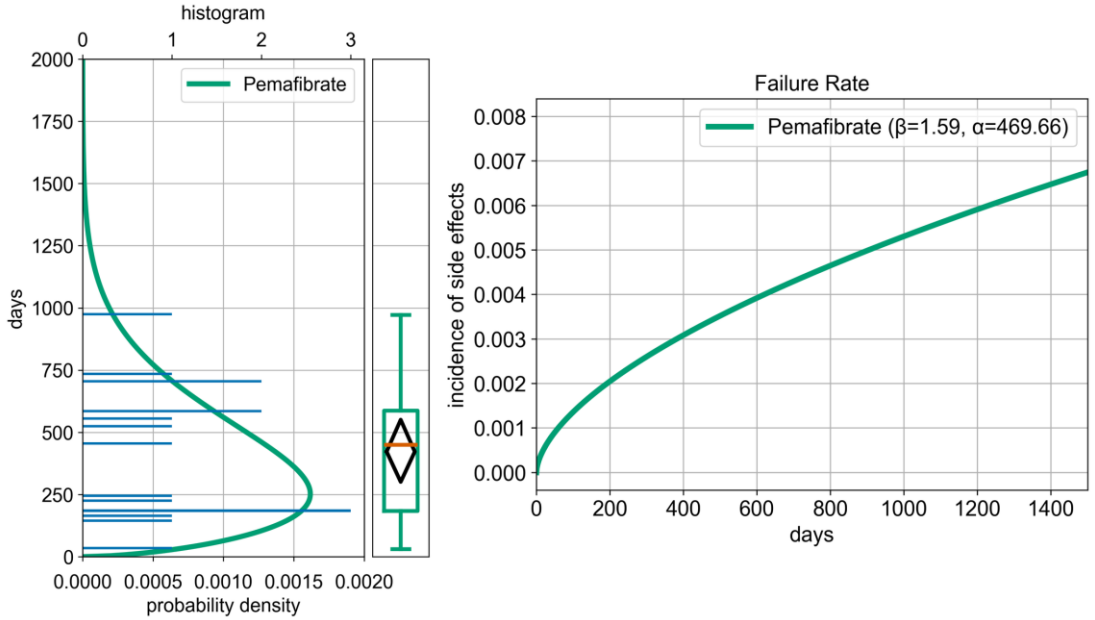


図4 JADERにおけるペマフィブラートの時系列解析結果

- JADERにおけるペマフィブラートのICSRのうち、開始日と発現日の双方が完全なデータは60.7%（N=17）であった
- 内訳は胆石症9例、胆嚢炎4例、急性胆嚢炎4例

表5 Weibullパラメータ推定結果

PTs	n	ß	α	median
cholelithiasis	9	2.05 [1.61–4.76]	485.93 [322.94–630.29]	525.0 [183.0–706.0]
Cholecystitis/ Cholecystitis acute	8	1.29 [0.87–2.94]	447.52 [223.36–705.30]	345.5 [149.0–706.0]
Overall	17	1.59 [1.17–2.56]	469.66 [327.34–613.50]	450.0 [185.0–587.0]

考察：報告の傾向について

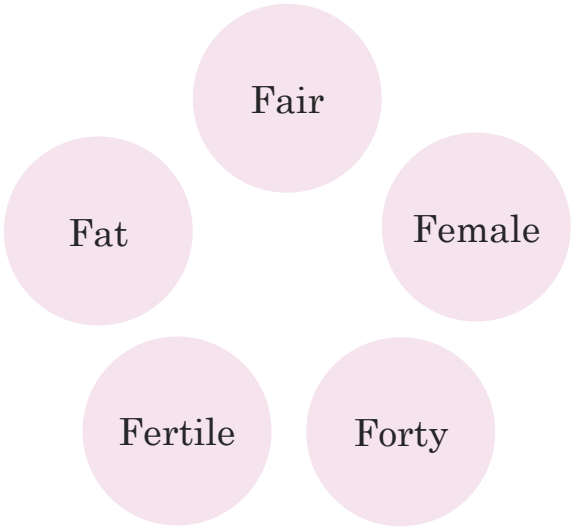
結果

- JADERでは男性の報告が多かった
- 報告は高齢層に偏っていた

考察

1. 処方動向による影響
2. 併存疾患の違いによる影響
3. 報告バイアス

〈胆石症のリスク因子〉

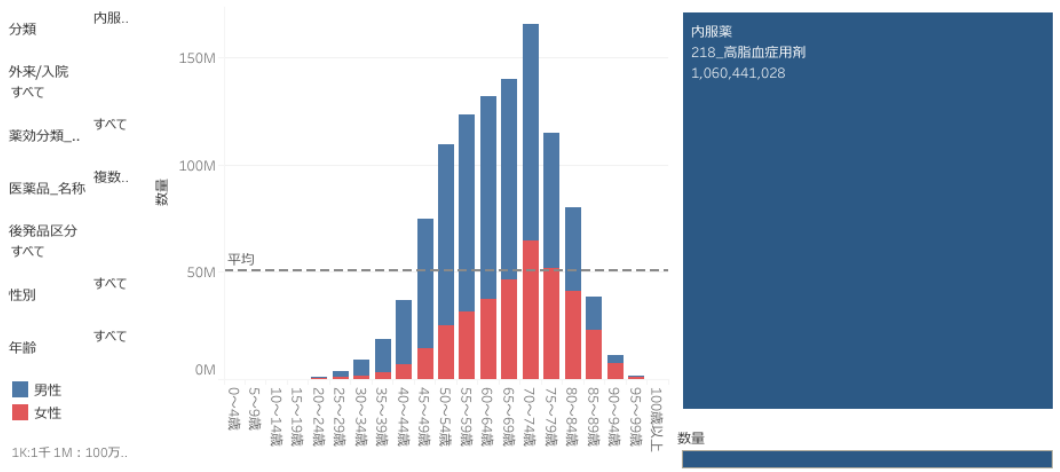


✓ 胆石のリスク因子は一般的に5Fと呼ばれ、Female（女性）、Forty（40歳代）、Fertile（多産）、Fat（肥満）、Fair（白人）が知られている[21]

胆嚢炎は胆石に起因することが多く、共通の危険因子を有する可能性が高いが、どの程度重複するかは明確でない

考察：処方動向および併存疾患による影響

1. 処方動向による影響



医薬品別数量

薬効分類_名称	後発品区分	医薬品_名称	
218_高脂血症用剤	0	610407028_ベザトールＳＲ錠１００ｍｇ	3,577,573
		620002123_ベザトールＳＲ錠２００ｍｇ	65,593,790
		622090701_リピディル錠５３．３ｍｇ	11,278,428
		622090801_リピディル錠８０ｍｇ	32,828,102
		622096801_トライコア錠５３．３ｍｇ	2,447,612
		622096901_トライコア錠８０ｍｇ	8,207,471
		622573101_パルモディア錠０．１ｍｇ	508,429,731

図5 処方数量

フィブラート系薬剤の処方数量は男性・高齢者の方が多い傾向がある

男性・高齢者の薬剤使用が多いことから男性・高齢者の有害事象報告が多いという可能性は十分高い

※ 医薬品としてフィブラート系薬剤（先発医薬品・後発医薬品どちらも含む）を選択

（出典：NDBオープンデータベース https://www.mhlw.go.jp/ndb/opendatasite/dai9kai/syohouyaku/sei_nennrei/index.html）

2. 併存疾患の違いによる影響

- 脂質異常症や2型糖尿病は胆石の危険因子として知られているが、日本においてこれらの疾患は男性により多い傾向がある（厚生労働省の国民健康・栄養調査より）

考察：主解析・層別解析について

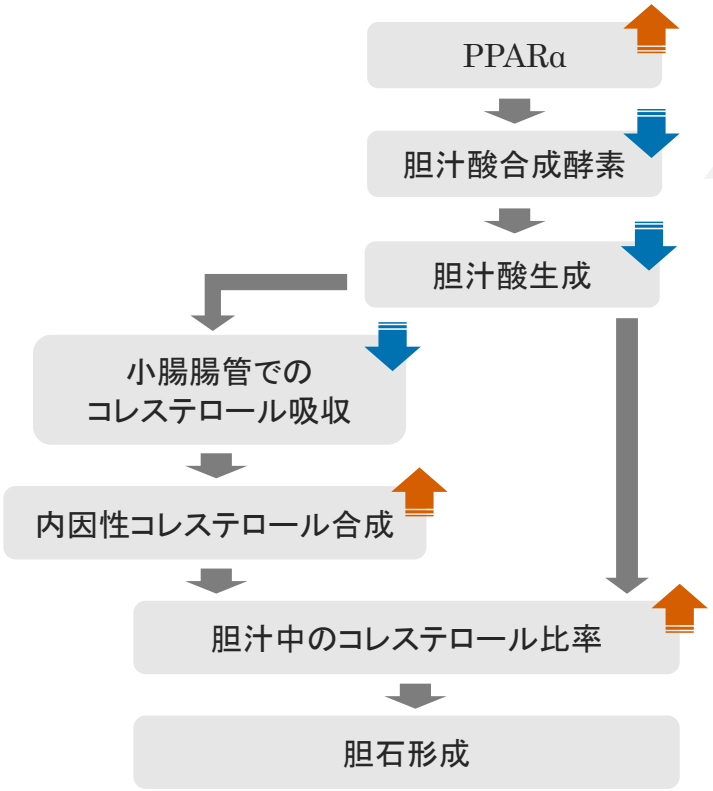
結果

- ペマフィブラートは4つのシグナル指標全て有意（層別解析でも全てのサブグループでシグナル確認）
- FAERSではベザフィブラートでもシグナルが検出された

考察

1. 作用機序の違いによるもの
2. 報告バイアス（新薬であるため報告が多い）
3. 国の背景差

1. 作用機序の違い



PPARαが胆汁酸合成律速酵素であるCYP7A1とCYP27A1の活性を抑制することで胆汁酸産生が低下する

- ペマフィブラートはこの作用がより強い可能性
- 選択性の低い他のフィブラート系薬剤とは異なる形で胆汁酸恒常性に影響し胆石形成を促進する可能性

今後の検証的研究が望まれる

考察：主解析・層別解析について

2. 報告バイアス

- JADERにおいて、ペマフィブラートは2018年に発売された新薬である
  - 新薬は注目されやすく、報告が集中しやすい傾向がある[22]
  - 発売後2年間は特に報告が集中しやすく、発売直後に報告が集中することはWeber効果と呼ばれている[23]

表6 ペマフィブラートの年別胆道系有害事象報告数 [%]

Year	Pemafibrate
2018	–
2019	6 [21.4]
2020	2 [7.1]
2021	7 [25.0]
2022	5 [17.9]
2023	3 [10.7]
2024	5 [17.9]

- 本研究における解析結果より、ペマフィブラートの胆道系有害事象は発売後から継続的に報告がされており、Weber効果の影響は少ないことが考えられる
- 新薬が報告されやすいというバイアスの影響は本研究結果からは判断できず、限界として残る

3. 国の背景差

- 肥満率の差として、日本の肥満率はBMI≥25が25.3%（BMI≥30：4.5%）に対し、米国の肥満率はBMI≥30が41.9%[24,25]
  - JADERは日本中心、FAERSは半数以上が米国からの報告であることから、これらの差異がシグナル検出に影響している可能性

考察：Time-to-onset解析（Weibull解析）

結果	考察
● ペマフィブラートの使用継続に伴い胆道有害事象の報告頻度が高くなる傾向がみられた ● 一方、一般的に胆石症の症状発現にかかる期間である2年よりも中央値は450日と短い[26]	● フィブラート系薬剤の作用によって、一般的な胆石形成よりも早期に胆石が形成される可能性 ● 早期の症例が報告されやすいというバイアスの影響[22]
● 急性胆嚢炎例の706日は急性発症としては異例に長い期間である	● 急性胆嚢炎の多くは胆嚢管の胆石閉塞によるため、胆石形成によって発症した可能性

- ✓ SRSの臨床情報は限定的であり、因果関係の推論は困難である
- ✓ ペマフィブラートは胆石症に禁忌であり、胆道系有害事象発現後には投与中止されることが多いことからも、患者の服用継続のためには胆石の評価を含む定期的な肝胆道系モニタリングが推奨される

〈本研究結果に基づくモニタリング時期の一例〉

治療開始から約6か月後から肝胆道モニタリングを開始。その後少なくとも年1回は継続して胆道系症状の聴取、肝機能検査、必要に応じて腹部超音波で胆石の有無を評価。患者背景に合わせて個別化することが前提。

今回症例数が17件と少なく、TTO解析の結果には頑健性があるとはいえない
今後さらなる研究が望まれる

結果：本研究結果と整合する症例報告

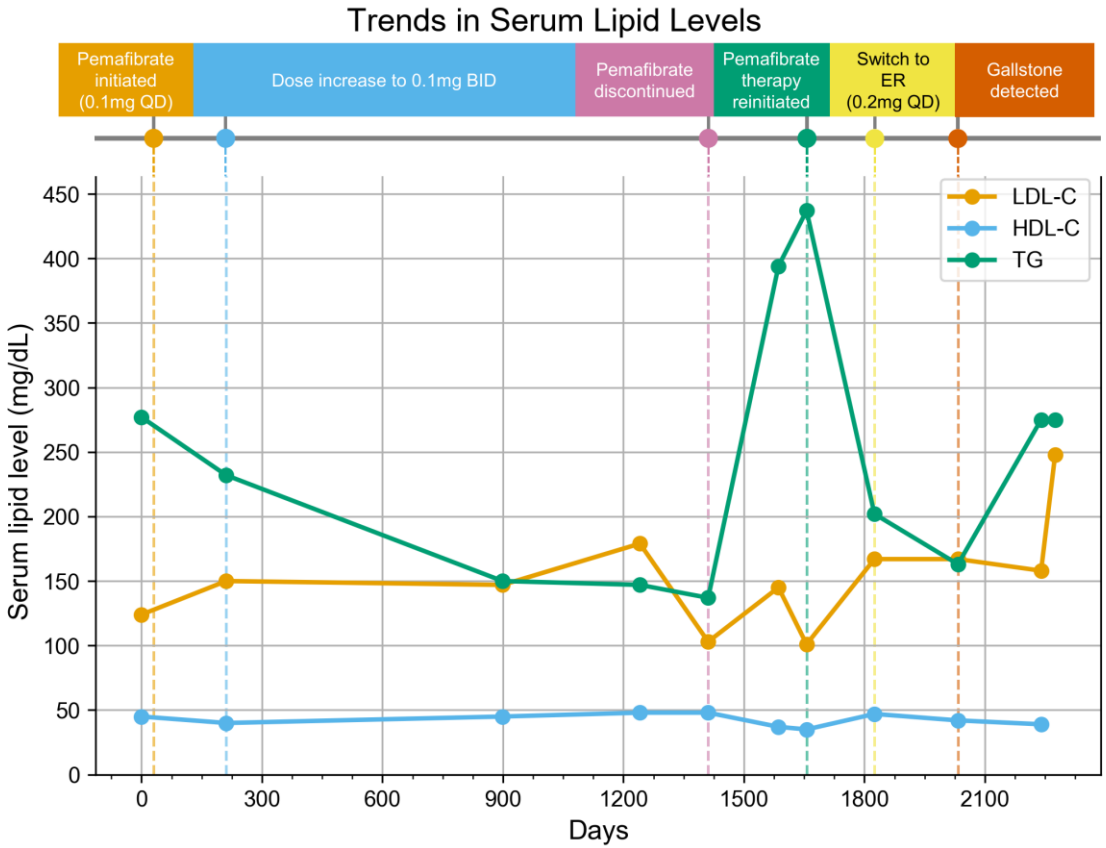


図4 症例患者の血清脂質値推移グラフ

高齢の日本人女性おける症例

- 投与は1日0.1mgから開始し、のちに0.2mg/日に増量
- 脂質改善を受けて3年10か月で中止し、8か月後に検査値悪化で服用再開。徐放性製剤への切り替えなども行われた
- 投与再開から1年後の健康診断にて超音波検査を実施した際に単発小胆石を検出、服用中止

〈患者が持つリスク因子〉

Female　Forty

- 総投与期間は約1760日
- 因果関係は証明されていないが、本研究のSRS解析では性別・年齢・BMIの各層で一貫して統計学的に有意な胆道系有害事象シグナルが示されている。本症例は臨床的に整合しており、ペマフィブラート関連有害事象である可能性は否定できない

考察：SRS解析の限界

表5 SRSにおけるバイアス[22]

バイアスの種類	概要
過少報告	大部分の副作用（中央値は約94%ともいわれる）が報告されない
重篤度バイアス	重篤な副作用ほど報告されやすい
新規性バイアス	新しい薬・新しい副作用ほど注目されやすく報告されやすい
刺激バイアス	メディア報道・学会発表・行政の注意喚起等の影響で報告が急増する
時間依存バイアス	薬が市場に出てからの期間によって報告数が変わる
地域・施設バイアス	報告者の地域・施設などによって報告傾向が異なる
適応症バイアス	使用される疾患や重症度によって副作用リスクや報告傾向が異なる
診断バイアス	副作用が既に知られている薬ではそれに注目して診断・報告されやすい

自発報告データベースは様々なバイアスがあり、因果の証明は困難である
今後の検証的研究が望まれる

結論

本研究の結論

フィブラート系薬剤と胆道系有害事象との関連が示唆された

まとめ

本研究の目的

自発報告システム（SRS）データベースを用いて、フィブラート系薬剤と胆道系有害事象との関連を評価する

本研究の結論

フィブラート系薬剤と胆道系有害事象との関連が示唆された

1 フィブラート間でのシグナル頑健性の違い

ペマフィブラートが最もシグナルの頑健性が認められ、フェノフィブラート、ベザフィブラートの順で頑健性が低下した

2 報告時期の傾向・推奨されるモニタリング時期

治療開始から約6か月後から肝胆道モニタリングを開始。その後少なくとも年1回は継続して胆道系症状の聴取、肝機能検査、必要に応じて腹部超音波で胆石の有無を評価する必要がある。患者背景に合わせて個別化することが前提（リスクの高い患者はより短いスパンで評価）

今後の展望

- シグナルがクラス効果か、薬剤特異的なものなのか、あるいは患者側リスク因子との相互作用なのかを切り分けるため、in vivo/in vitroの機序研究を進める必要性
- 交絡を十分に調整できるコホート研究を実施し、絶対リスクやサブグループ差を定量化

▼

ファーマコビジランスと観察・機序研究の統合により、
仮説生成段階の所見を臨床的に実装可能なエビデンスへと高める

本研究は、以下の国際学術誌に採択されています。

論文情報

Title：
Disproportionality Analysis of Biliary Adverse Events Associated with Fibrates Using the JADER and FAERS Databases

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Disproportionality Analysis of Biliary Adverse Events Associated with Fibrates Using the JADER and FAERS Databases

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Scope Statement

This manuscript examines biliary adverse events associated with fibrates using large pharmacovigilance databases and clarifies why the work fits within the scope of Frontiers in Pharmacology. We performed disproportionality analyses in the Japanese Adverse Drug Event Report (JADER) and the U.S. FDA Adverse Event Reporting System (FAERS), harmonized MedDRA terms for biliary outcomes, and applied established signal detection metrics with sensitivity checks. The use of two independent spontaneous reporting systems was intended to confirm the robustness and reproducibility of detected signals across datasets generated in different settings. Consistent patterns between JADER and FAERS increase confidence in the findings. The study highlights clinically relevant contexts where vigilance during fibrate therapy may be warranted and provides transparent, reproducible methods. Where appropriate, we conducted stratified analyses and time-to-onset modeling to characterize signals more comprehensively; all analyses were based on prespecified criteria with rigorous data curation. Although spontaneous reporting cannot prove causality, convergent results from independent sources yield actionable, real-world evidence for clinicians, pharmacovigilance specialists, and regulatory decision-makers. Overall, the work aligns with the journal's aims by advancing drug safety science with methodologically rigorous, robust, and practice-informing evidence derived from post-marketing data.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

Credit Author Statement

Taro Watanabe: Writing – review & editing. **Hidenori Sagara**: Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Validation, Writing – review & editing. **Naoto Okada**: Writing – review & editing. **Kyosuke Nagura**: Data curation, Methodology, Software, Validation, Writing – review & editing. **Satoko Watanabe**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Visualization, Writing – original draft, Writing – review & editing.

Keywords

fibrates, Pemafibrate, Biliary adverse events, Pharmacovigilance, Disproportionality analysis, Time-to-onset analysis, JADER, FAERS

Abstract

Word count: 236

Introduction: Fibrates are effective triglyceride-lowering drugs, but they may affect bile acid metabolism, raising concerns about biliary adverse drug events (ADEs). Objective: In this study, we used spontaneous reporting system databases to evaluate the association between fibrates and biliary ADEs. This study has been reported in accordance with the Reporting of a Disproportionality Analysis for Drug Safety Signal Detection Using Individual Case Safety Reports in PharmacoVigilance guidelines. Methods: We used data from the Japanese Adverse Drug–Event Report (JADER) and the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) databases. The signal detection metrics employed were reporting odds ratio (ROR), proportional reporting ratio, Bayesian confidence propagation neural network, and Gamma–Poisson Shrinker. We also conducted stratified disproportionality and time-to-onset analyses. Results: We identified 58 and 260 unique individual case safety reports from the JADER and FAERS databases, respectively. Primary disproportionality analysis of all fibrates in the JADER dataset revealed an ROR of 3.74 [2.88–4.85]. All other signal detection metrics also exhibited statistically significant associations. In the stratified disproportionality analysis, pemafibrate showed significant signals across all strata, confirming the robustness of the signal. In the Weibull analysis for pemafibrate, the shape parameter (β) was 1.59 [1.17–2.56], indicating an increasing trend in ADE reporting with continued pemafibrate use. Conclusion: A significant signal for biliary ADEs was detected for fibrates in both databases, with a particularly consistent association for pemafibrate. Regular hepatobiliary monitoring and individualized patient management are recommended.

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Ethics statements

Studies involving animal subjects
Generated Statement: No animal studies are presented in this manuscript.

Studies involving human subjects
Generated Statement: Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Inclusion of identifiable human data
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Data availability statement

Generated Statement: Publicly available datasets were analyzed in this study. This data can be found here: **JADER data are available from the PMDA website (https://www.pmda.go.jp/safety/info-services/drugs/adr-info/suspected-adr/0003.html) FAERS data are available from the FDA website (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html)**.

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The author(s) verify and take full responsibility for the use of generative AI in the preparation of this manuscript. Generative AI was used

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Disproportionality Analysis of Biliary Adverse Events Associated with Fibrates Using the JADER and FAERS Databases

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Abstract

Introduction: Fibrates are effective triglyceride-lowering drugs, but they may affect bile acid metabolism, raising concerns about biliary adverse drug events (ADEs).

Objective: In this study, we used spontaneous reporting system databases to evaluate the association between fibrates and biliary ADEs. This study has been reported in accordance with the Reporting of a Disproportionality Analysis for Drug Safety Signal Detection Using Individual Case Safety Reports in PharmacoVigilance guidelines.

Methods: We used data from the Japanese Adverse Drug–Event Report (JADER) and the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) databases. The signal detection metrics employed were reporting odds ratio (ROR), proportional reporting ratio, Bayesian confidence propagation neural network, and Gamma–Poisson Shrinker. We also conducted stratified disproportionality and time-to-onset analyses.

Results: We identified 58 and 260 unique individual case safety reports from the JADER and FAERS databases, respectively. Primary disproportionality analysis of all fibrates in the JADER dataset revealed an ROR of 3.74 [2.88–4.85]. All other signal detection metrics also exhibited statistically significant associations. In the stratified disproportionality analysis, pemafibrate showed significant signals across all strata, confirming the robustness of the signal. In the Weibull analysis for pemafibrate, the shape parameter (β) was 1.59 [1.17–2.56], indicating an increasing trend in ADE reporting with continued pemafibrate use.

Conclusion: A significant signal for biliary ADEs was detected for fibrates in both databases, with a particularly consistent association for pemafibrate. Regular hepatobiliary monitoring and individualized patient management are recommended.

1 Introduction

Fibrates are widely used to lower triglyceride levels. Their mechanism of action involves the activation of peroxisome proliferator–activated receptors (PPARs), a family of transcription factors in the nuclear hormone receptor superfamily (Staels et al., 1998). Of the three PPAR subtypes (α, β/δ, γ), PPARα primarily mediates the lowering of triglyceride levels (Staels et al., 1998).

PPARα suppresses the activity of CYP7A1 and CYP27A1, the rate-limiting enzymes in bile acid synthesis (Post et al., 2001; Ghonem et al., 2015), leading to a decrease in bile acid production and the likely development of biliary tract–related adverse effects, including cholelithiasis (Post et al., 2001). A case series suggested an association between fibrates use and cholelithiasis (Caroli-Bosc et al., 2001). A 52-week Phase III trial of pemafibrate reported a cholelithiasis incidence of 5.3% (Kowa Co., 2024). Pemafibrate is a selective PPARα modulator approved in Japan in 2017 (Kowa Co., 2024).

Evidence linking fibrates to biliary adverse drug events (ADEs) remains limited. Clinical trials are conducted under controlled conditions and may not reflect real-world practice (Singh and Loke, 2012). Post-marketing, high-quality prospective studies on biliary ADEs are scarce, particularly in older adults and individuals on multiple medications (Cohen et al., 2024). Moreover, the use of pemafibrate is currently confined to a few countries, including Japan, Singapore, and Thailand, resulting in a paucity of data on adverse events.

Spontaneous reporting systems (SRSs) are increasingly being used in drug safety evaluation (Alomar et al., 2020). Understanding drug safety warrants multiple data sources in addition to clinical trials (Singh and Loke, 2012). SRS databases provide complementary information, especially for drugs with limited use, such as pemafibrate (Noguchi et al., 2021). The Japanese Adverse Drug–Event Report (JADER) and the Food and Drug Administration Adverse Event Reporting System (FAERS) are two of the prominent SRS databases available.

In this hypothesis-generating study, we examined the association between fibrates and biliary tract ADEs using JADER and FAERS. The study aimed to detect potential safety signals and describe disproportionality and reporting patterns to inform future pharmacoepidemiologic research.

2 Materials and Methods

2.1 Database Sources

Individual case safety reports (ICSRs) were obtained from the JADER database, maintained by the Pharmaceuticals and Medical Devices Agency (PMDA). Reports were also obtained from the FAERS database, maintained by the U.S. Food and Drug Administration (FDA). Data were downloaded from the official PMDA and FDA websites. The data snapshots were as follows: JADER (downloaded June 6, 2025) and FAERS (quarterly files through 2024 Q4; compiled dataset last updated on June 16, 2025). The JADER dataset covered April 2004 to May 2025. The FAERS dataset covered Q1 2014 to Q4 2024.

In the JADER dataset, the DRUG and HIST tables were left-merged with the DEMO table to create a patient-level dataset (Figure 1). In the FAERS dataset, duplicate reports were removed by keeping the record with the highest case version number in the DEMO table. The DRUG and DEMO tables were then left-merged to create a patient-level dataset. The OUTC table was merged for disproportionality analyses, and the THER table was merged for time-to-onset (TTO) analysis.

2.2 Identification of Individual Case Safety Reports Involving Fibrates and Biliary Adverse Drug Events

To identify fibrate-related reports in the JADER dataset, we used the Japanese generic names for pemafibrate, fenofibrate, and bezafibrate. In the FAERS dataset, we searched for "PEMAFIBRATE," "FENOFIBRATE," "FENOFIBRIC ACID," "CHOLINE FENOFIBRATE," and "BEZAFIBRATE," standardizing the spelling variations of "Fenofibrate." We included all drug–event pairs in which a fibrate was listed in any drug role (e.g., suspect, concomitant, or interacting) to avoid reporting bias. We also conducted a sensitivity analysis in which the disproportionality analysis was limited to primary suspect drugs. We defined a drug–event pair as a unique combination of one drug and one adverse event. When a single ICSR contained multiple drugs or events, all possible combinations of these were counted as separate pairs. Because a single ICSR may include multiple fibrates (e.g., concomitant use or drug switching), agent-level counts are not mutually exclusive. The overall total for "all fibrates" reflects unique ICSRs. Consequently, the sum of agent-level counts may not equal the overall total.

Biliary events were identified using the Japanese translation of the Medical Dictionary for Regulatory Activities, version 28.0. Fourteen preferred terms under the high-level term "Cholecystitis and cholelithiasis" (10008616) were included (Supplementary Table 1).

2.3 Primary Disproportionality Analysis

For signal detection, we constructed a 2×2 contingency table (Table 1).

n11 represented drug–event pairs involving fibrates and cholecystitis or cholelithiasis; n12 represented drug–event pairs involving fibrates without these events; n21 represented drug–event pairs involving these events without fibrates; and n22 represented drug–event pairs involving neither. We calculated the reporting odds ratio (ROR) and proportional reporting ratio (PRR). We also calculated the information component (IC) using the Bayesian confidence propagation neural network and the empirical Bayes geometric mean (EBGM) using the Gamma–Poisson Shrinker estimator.

ROR, a sensitive screening metric, is a standard metric in JADER (Sakaeda et al., 2013). A signal was considered present when $n11 \geq 3$ and ROR025, the lower bound of the 95% confidence interval (95% CI), exceeded 1. P values were obtained using Fisher's exact test.

PRR compares the event proportion for a drug against all other drugs, and it follows the implementation of the Medicines and Healthcare products Regulatory Agency (Evans et al., 2001). PRR025, the lower bound of the 95% CI, was used to more strictly evaluate drugs that had passed ROR-based initial screening. While this higher threshold can reduce false positives, it may also increase the risk of missing important signals (Harpaz et al., 2013). A signal was considered present when $n11 \geq 3$, PRR025 > 2, and the chi-square (χ^2) statistic > 4.

The Bayesian confidence propagation neural network is a Bayesian approach that stabilizes estimates for sparse data (Bate et al., 1998; Orre et al., 2000). A signal was considered present when IC025, the lower bound of the 95% credibility interval of IC, exceeded 0.

The Gamma–Poisson Shrinker estimator uses empirical Bayes shrinkage with stratification (Dumouchel, 1999; Szarfman et al., 2002, 2004). In the JADER dataset, EBGM was estimated using a stratified model. Reports were stratified by sex (male/female) and age group (≥ 60 vs. 20–50 years). Expected counts within each stratum were computed under the independence assumption and pooled across strata to obtain the EBGM and its 90% CI. A signal was considered present when EBGM05, the lower bound of the 90% CI, was equal to or greater than 2.0. EBGM was not computed for FAERS data because stratification was not performed.

The formulas used, confidence intervals computed, and parameter settings applied are provided in Supplementary Methods 1.

2.4 Stratified Disproportionality Analysis

Stratified analysis was performed for sex, age, and body mass index (BMI). Sex was categorized as male or female, age as ≥60 years or 20–50 years, and BMI as ≥25 or <25. For calculating BMI, the median value for each height and weight category was used, given that JADER records these in 10-cm and 10-kg increments. Reports with missing data for the target stratum were excluded.

Stratified analysis was not performed on FAERS data. Pemafibrate use is concentrated in Japan and a few other countries; therefore, only a few reports were available on the FAERS database (Arai et al., 2024), precluding BMI calculation.

2.5 Time-to-onset Analysis

TTO analysis was limited to pemafibrate data from the JADER dataset with complete therapy-start and event onset dates (N = 17); reports with incomplete or ambiguous dates were excluded. TTO was defined as the number of days from drug initiation to event onset, with one day added to avoid zero-day values when the event occurred on the start date (Ando et al., 2019). The descriptive statistics for TTO analysis included median, first quartile, third quartile, maximum, and minimum. A box-and-whisker plot was generated.

For Weibull analysis, the shape (β) and scale (α) parameters were estimated using maximum likelihood estimation, and the Weibull curve was plotted. Because only 17 reports contained complete date information, 95% CIs for α and β were calculated through bootstrapping (Estadística et al., 2018). β was interpreted as wear-out if the lower bound >1, random if the interval included 1, and early failure if the upper bound <1 (Leroy et al., 2014).

2.6 Analytical Tools and Software Environment

Analyses were performed using the MSIP platform (version 1.10.1; NTT DATA Mathematical Systems Inc., Tokyo, Japan) and the Python programming language (version 3.13). ChatGPT (OpenAI, GPT-5, https://chat.openai.com/) was used to support the generation of some Python prompts for figure preparation; all outputs were reviewed and verified by the authors. This study has been reported in accordance with the Reporting of a Disproportionality Analysis for Drug Safety Signal Detection Using ICSRs in PharmacoVigilance guidelines (Fusaroli et al., 2024a, 2024b).

The requirement for an institutional ethics review was waived because the study used publicly available, de-identified data (see Ethics Statement).

2.7 Ethics Statement

This study analyzed publicly available, de-identified reports from the JADER and FAERS databases; therefore, approval from the institutional review board was not required. For the clinical vignette, all potentially identifiable information was removed, and patient consent for publication was obtained.

3 Results

3.1 Basic Characteristics of the Individual Case Safety Reports

In the JADER dataset, the proportion of male ICSRs was 67.9% for pemafibrate, 70.0% for fenofibrate, and 69.2% for bezafibrate (Table 2). ICSRs from individuals aged ≥60 years accounted for 67.9% of the pemafibrate reports, 80.0% of the fenofibrate reports, and 61.5% of the bezafibrate reports. Among the fenofibrate ICSRs, only one was submitted by a consumer; all other reports, including those for pemafibrate and bezafibrate, came from healthcare professionals.

3.2 Primary Disproportionality Analysis

A total of 58 unique ICSRs were identified from the JADER dataset. Pemafibrate was involved in 28 drug–event pairs, fenofibrate in 20 pairs, and bezafibrate in 13 pairs (Figure 2). For all fibrates combined, the ROR was 3.74 (95% CI, 2.88–4.85; $P < 0.01$), PRR was 3.71 (95% CI, 2.86–4.81; $\chi^2 > 4$), IC was 1.80 (95% CI, 1.42–2.19), and EBGM was 3.37 (90% CI, 2.93–3.85), with all metrics indicating statistically significant associations. By agent, pemafibrate and fenofibrate showed significant signals across all metrics, whereas no significant signals were observed for bezafibrate.

A total of 260 unique ICSRs were identified from the FAERS dataset. Pemafibrate was involved in 3 drug–event pairs, fenofibrate in 233 pairs, and bezafibrate in 25 pairs. For all fibrates, the ROR was 3.81 (95% CI, 3.37–4.31; $P < 0.01$), PRR was 3.79 (95% CI, 3.36–4.28; $\chi^2 > 4$), and IC was 1.91 (95% CI, 1.79–2.04), with all metrics showing statistical significance. Signals for ROR and PRR were observed for pemafibrate, while fenofibrate and bezafibrate showed significant signals for ROR, PRR, and IC.

In a sensitivity analysis restricted to primary suspect drugs using the JADER dataset, statistically significant disproportionality was observed for all fibrates combined (N = 36; ROR 10.44 [95% CI 7.48–14.58], PRR 10.19 [95% CI 7.37–14.10], IC 3.01 [95% CI 2.53–3.50]). By agent, the signal was retained for pemafibrate and fenofibrate but not for bezafibrate. In FAERS, all fibrates combined also showed statistically significant disproportionality (N = 67; ROR 6.28 [95% CI 4.94–8.00], PRR 6.22 [95% CI 4.90–7.89], IC 2.53 [95% CI 2.18–2.88]). By agent, the signal was retained for fenofibrate and not retained for bezafibrate; pemafibrate had no primary suspect cases (N = 0), so signal estimation was not applicable.

The detailed results are summarized in Supplementary Table 2 and 3.

3.3 Stratified Disproportionality Analysis

For pemafibrate, significant ROR, PRR, and IC signals were detected in all strata (Figure 3). For fenofibrate, significant ROR and IC signals were found in the male, female, and age ≥60 years strata, whereas PRR was significant only in the male and age ≥60 years strata. No significant signals were

detected for fenofibrate in BMI-based subgroups. For bezafibrate, a significant ROR signal was observed only in the BMI ≥25 stratum. No other significant signals were detected. The detailed stratified results are provided in Supplementary Table 4.

3.4 Time-to-onset Analysis

In the JADER dataset, TTO data were available only for 60.7% of the pemafibrate ICSRs (N = 17). The events in question comprised nine cases of cholelithiasis, four of cholecystitis, and four of acute cholecystitis (Table 3).

For all cases: $\alpha = 469.66$ (95% CI, 327.34–613.50), $\beta = 1.59$ (95% CI, 1.17–2.56) (Figure 4). The median TTO was 450.0 days (95% CI, 185.0–587.0), with an interquartile range of 185.0–587.0 days.

For cholelithiasis: $\alpha = 485.93$ (95% CI, 322.94–630.29), $\beta = 2.05$ (95% CI, 1.61–4.76). The median TTO was 525.0 days (95% CI, 183.0–706.0).

For cholecystitis and acute cholecystitis: $\alpha = 447.52$ (95% CI, 223.36–705.30), $\beta = 1.29$ (95% CI, 0.87–2.94). The median TTO was 345.5 days (95% CI, 149.0–706.0).

4 Discussion

4.1 Basic Characteristics of the Individual Case Safety Reports

This study analyzed preferred terms for cholecystitis and cholelithiasis.

Cholelithiasis is commonly associated with the "5 Fs"—Fair, Fat, Female, Fertile, and Forty—reflecting the higher prevalence encountered in middle-aged women (Bass et al., 2013). Because cholecystitis often arises from gallstones, the two conditions likely share risk factors, although the degree of overlap remains uncertain.

In the JADER dataset, male ICSRs exceeded female ICSRs, contrasting with the known epidemiology of gallstone disease, whereas the skew toward older ages was consistent (Bass et al., 2013). Possible explanations include prescribing patterns—triglyceride-lowering drugs are more often prescribed to men and middle-aged or older adults in Japan (Ministry of Health, Labour and Welfare, 2025)—and reporting bias, where physicians may be more likely to suspect a drug-related cause in men. Similarly, in NDB open data, fibrate prescriptions are concentrated in these age groups and are more commonly prescribed to men (Ministry of Health, Labour and Welfare, 2025). Note that the number of cases represents the number of prescriptions, not the number of patients.

Differences in comorbidity profiles may also contribute to this trend. Metabolic syndrome and type 2 diabetes, both established risk factors for gallstones (Méndez-Sánchez et al., 2005; Aune and Vatten, 2016), are more prevalent in Japanese men (Ministry of Health, Labour and Welfare, 2025). Given that comorbidity data in JADER are often incomplete, population-based cohort studies including both drug-exposed and unexposed individuals are needed to distinguish drug effects from metabolic risk.

4.2 Disproportionality Analyses

Primary disproportionality analysis conducted on the JADER dataset detected clear biliary tract disease signals for fibrates. Pemafibrate showed significant disproportionality across ROR, PRR, IC,

and EBGM, with stratified analysis confirming consistent signals in all subgroups. These findings suggest an association between fibrates and biliary ADEs.

In the JADER dataset, consistent signals were observed for pemafibrate, while fewer signals were detected for fenofibrate and bezafibrate, respectively. The presence or absence of such signals may reflect not only pharmacological characteristics, such as PPARα selectivity, but also differences in patient characteristics, including demographic, genetic, and metabolic factors.

Pemafibrate has a markedly higher selectivity for PPARα than other fibrates while retaining strong triglyceride-lowering effects (Honda et al., 2022). PPARα agonism can lower bile acid output by reducing CYP7A1 activity and CYP27A1 mRNA levels (Post et al., 2001; Ghonem et al., 2015). Mechanistically, PPARα agonists diminish HNF-4α binding to the DR-1 element on the CYP7A1 promoter, and PPARα may antagonize LXR-dependent activation of CYP7A1 (Marrapodi and Chiang, 2000; Rakhshandehroo et al., 2010). Beyond effects on total output, bile acid composition is partly governed by CYP8B1. PPARα activation increases hepatic CYP8B1, thereby raising 12α-hydroxylated bile acids and the CA/CDCA ratio (Chiang, 2004; Xie et al., 2019). Because CA-rich bile is generally more cholesterol-saturated than CDCA-rich bile, this shift may increase the cholesterol saturation index (CSI) and the risk of cholesterol gallstones (Einarsson and Grundy, 1980). Given its high selectivity for PPARα, pemafibrate may amplify these pathways and alter bile acid homeostasis, potentially increasing gallstone risk.

Further research is needed to determine whether this represents a class effect, a drug-specific phenomenon, or an interaction with patient risk factors. Mechanistic *in vivo* and *in vitro* studies could clarify how pemafibrate alters bile acid synthesis and cholesterol saturation. Large population-based cohorts are also necessary to quantify risk and adjust for confounding factors. Integrating pharmacovigilance data with observational and mechanistic studies will be essential for evidence-based prescribing and monitoring.

In the United States (U.S.), adult obesity (BMI ≥30: 41.9%) exceeds that in Japan (BMI ≥25: 25.3%; ≥30: 4.5%) (Stierman et al., 2021; Ministry of Health, Labour and Welfare, 2025), indicating a higher baseline risk of gallstones in the U.S. Even so, a signal was detected in Japan's JADER database, suggesting drug-related contributions to reported gallstone disease and cholecystitis. Cross-country differences in prescribing likely influenced signal detection. In Japan, fenofibrate and bezafibrate have long been used, and pemafibrate use has increased since its approval. In the U.S., fenofibrate predominates, whereas bezafibrate and pemafibrate are not approved (Jackevicius et al., 2011; Arai et al., 2024). FAERS reporting is U.S.-centric, and the case counts (N) in the primary analysis likely reflect this exposure distribution.

4.3 Time-to-onset Analysis

TTO analysis helps identify temporal patterns in the development of ADEs (Leroy et al., 2014). Because gallstones may remain asymptomatic for over 2 years (Mok et al., 1986), TTO in SRSs often reflects diagnosis or symptom onset rather than true onset (Leroy et al., 2014).

In this study, Weibull analysis suggested an increasing risk of biliary ADEs with prolonged pemafibrate use. The median TTO was 450 days (95% CI, 185.0–587.0), which is shorter than that reported in previous studies (Mok et al., 1986), possibly owing to fibrate pharmacology and early-reporting bias in SRSs (Goldman, 1998).

Seven cholecystitis cases were identified (four acute, three unspecified). The acute cases showed a wide TTO range (31–706 days), with the upper bound unusually high for an acute presentation. Most acute cholecystitis cases result from cystic duct obstruction by gallstones (Gallaher and Charles, 2022), suggesting that gallstone formation may have preceded inflammation. However, the limited clinical data in SRSs precludes causal inferences. Given that pemafibrate is contraindicated in patients with cholelithiasis (Kowa Co., 2024) and often discontinued after biliary ADEs, regular hepatobiliary monitoring, including gallstone assessment, is recommended. Based on the median TTO of about 450 days in this study, starting hepatobiliary monitoring around 6 months after treatment begins and continuing it at least once a year seems reasonable. Monitoring should include checking for biliary symptoms, liver function tests, and abdominal ultrasonography when needed. These findings should be interpreted with caution because the Weibull analysis was based on a small number of cases. More work is needed to better define the optimal timing, frequency, and approach to monitoring.

While caution is warranted regarding the potential biliary risks associated with fibrate-class drugs, these agents have demonstrated cardiovascular benefits in patients with dyslipidemia (Jun et al., 2010). Therefore, clinicians should carefully weigh the cardiovascular benefits against the biliary risks and tailor treatment and monitoring strategies to individual patients.

4.4 Case in Clinical Practice

We report a real-world case of gallstone detection after long-term pemafibrate use in an elderly Japanese woman (Figure 5). She switched from ezetimibe to pemafibrate at an initial daily dosage of 0.1 mg, which was subsequently increased to 0.2 mg daily. The treatment was stopped after 3 years and 10 months after her lipid levels improved. The treatment was resumed 8 months later using the extended-release tablet.

One year after resuming treatment, a routine ultrasound revealed a single small gallstone. She had no history of cholelithiasis and was asymptomatic. The only risk factors identified were female sex and age >40 years. The total duration of pemafibrate treatment was approximately 1,760 days.

Although causality is unproven, a pemafibrate-associated ADE cannot be excluded as a possible etiology of the patient's condition. Our SRS analysis found consistent, significant biliary ADE signals across sex, age, and BMI strata. This case is clinically consistent with those findings and highlights the need to reassess biliary ADE risk with long-term fibrate use. In elderly patients, gallstones often remain asymptomatic; therefore, regular imaging-based monitoring should be considered regardless of symptoms.

4.5 Limitations

Although SRSs are useful for early signal detection and post-marketing surveillance (Montastruc et al., 2006), they have some limitations (Kasliwal, 2012; Noguchi et al., 2021). Underreporting is substantial, with a median rate of nearly 94% (Hazell and Shakir, 2006). Reporting bias is common, with peaks observed soon after drug approval (Weber effect) (Weber, 1987; Raschi et al., 2013) and increases in reporting following label warnings or publications (notoriety bias) (Pariente et al., 2007). Pemafibrate was launched in Japan in 2018, and its safety data may have been influenced by the Weber effect. However, continuous reporting of cholecystitis and cholelithiasis was observed without early clustering, suggesting only a limited impact of the Weber effect. Nevertheless, its potential influence cannot be completely excluded due to the inherent characteristics of SRS data. Severe or novel events also tend to be selectively reported (Hazell and Shakir, 2006; Matsuda et al., 2015).

Data on key patient characteristics are often missing (Dang et al., 2022), which limits adjustment for confounding factors. Furthermore, known gallstone risk factors (obesity, female sex, and diabetes) were more frequent among patients treated with fibrates, and this imbalance may have contributed to the observed signals. Incidence rates cannot be calculated because only patients with ADEs are included (Goldman, 1998).

These sources of bias and confounding factors cannot be adequately controlled in SRS analyses. Therefore, findings should be interpreted as indicators of disproportional reporting rather than evidence of causality. For some drug–event combinations in this study, the number of cases was small, resulting in limited statistical power and wide uncertainty in the estimates. The time-to-onset assessment relied on only 17 cases with complete date information and did not account for the effects of treatment discontinuation or dose adjustments. Consequently, these results should be regarded as hypothesis-generating and require confirmation in larger, well-designed studies.

5 Conclusion

This study suggests an association between fibrates and biliary ADEs, particularly cholecystitis and cholelithiasis.

These findings provide valuable insights to guide future mechanistic and epidemiological studies. In clinical practice, careful attention should be paid to biliary ADEs during fibrate therapy. Regular hepatobiliary monitoring should be tailored to the patient's background and maintained throughout treatment.

6 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

7 Author Contributions

Conceptualization: S.W., H.S. Methodology: S.W., K.N., H.S. Data curation: S.W., K.N. Formal analysis: S.W. Software: S.W., K.N. Visualization: S.W. Investigation: S.W. Validation: K.N., H.S. Writing—original draft: S.W. Writing—review & editing: S.W., K.N., N.O., T.W., H.S. Resources: H.S. Funding acquisition: H.S. Supervision: H.S.

All authors approved the final manuscript.

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11 Data Availability Statement

The data underlying this study are publicly available. JADER data can be obtained from the PMDA website and FAERS data from the FDA website. The list of Preferred Terms from the Japanese Translation of the Medical Dictionary of Regulatory Activities used to define biliary events is provided in Supplementary Table 1. All analysis code used to compute the metrics from the 2 × 2 counts and to generate figures is openly available at: https://github.com/p120119/fibrates-biliaryADEs_SRS_analysis/releases/tag/v1.0.0.

12 Figure Legends

Figure 1. Flowchart of Data Analysis of JADER and FAERS Data

This flowchart shows the series of steps involved in data preprocessing, case selection, and signal detection in the JADER and FAERS datasets.

JADER: Japanese Adverse Drug–Event Report database; FAERS: Food and Drug Administration Adverse Event Reporting System; Q1: first quarter; Q4: fourth quarter; ICSRs: individual case safety reports; ROR: reporting odds ratio; PRR: proportional reporting ratio; BCPNN: Bayesian confidence propagation neural network; GPS: Gamma–Poisson Shrinker

Figure 2. Results of Primary Disproportionality Analysis of JADER and FAERS Data

This figure presents the results of the primary disproportionality analysis conducted on the JADER and FAERS datasets. A check mark indicates a statistically significant signal. N (per-drug) = drug–event pairs. "Overall" = unique ICSRs. Per-drug counts are not mutually exclusive; therefore the total may not equal the sum across drugs.

IC: information component; EBGM: empirical Bayes geometric mean; PRR025: lower bound of the 95% confidence interval for PRR; IC025: lower bound of the 95% confidence interval for IC; EBGM05: lower bound of the 90% confidence interval for EBGM.

Figure 3. Results of Stratified Disproportionality Analysis of JADER Data

This figure presents the results of stratified disproportionality analysis for each fibrate in the JADER database. Drug–event pairs were extracted for each subgroup—sex (male and female), age (≥60 years and 20–50 years), and BMI (≥25 and <25)—and disproportionality analysis was performed separately for each. A check mark indicates a statistically significant signal.

Figure 4. Weibull Distribution and Box Plot Based on Time-to-Onset Analysis of Cholecystitis and Cholelithiasis

Time-to-onset analysis for pemafibrate in the JADER dataset (N = 17); complete date reports only. Median (IQR) are shown; shaded band = 95% CI for the Weibull shape parameter (β).

(A) Histogram, Weibull distribution curve, and box plot based on time-to-onset (TTO) data. The histogram was created using the number of ICSRs, and the Weibull distribution curve was overlaid.

(B) Failure rate distribution. The Weibull shape parameter (β) exceeded 1, indicating an increasing failure rate over time—a wear-out failure type.

Figure 5. Treatment Timeline and Trends in Serum Lipid Levels

Vertical dashed lines indicate major clinical events during the treatment course, and the lines represent LDL-C (orange), HDL-C (blue), and TG (green) levels at each measurement point. The x-axis shows the date, and the y-axis shows serum lipid levels (mg/dL).

QD: quaque die (once daily), BID: bis in die (twice daily), ER: extended-release

13 Tables

Table 1. 2×2 contingency table

	Target adverse drug–event	Other adverse drug events	Sums
Fibrates	n11	n12	n1+
Other drugs	n21	n22	n2+
Sums	n+1	n+2	n++

A 2×2 contingency table was constructed using fibrates as the drugs of interest and biliary ADEs (defined by 14 PTs under the HLT "Cholecystitis and cholelithiasis") as the events of interest.

n11: drug–event pairs that involved fibrate use and indicated cholecystitis or cholelithiasis

n12: drug–event pairs that involved fibrate use and did not indicate cholecystitis or cholelithiasis

n21: drug–event pairs that did not involve fibrate use but indicated cholecystitis or cholelithiasis

n22: drug–event pairs that did not involve fibrate use and did not indicate cholecystitis or cholelithiasis

PTs: Preferred Terms; HLT: high-level term.

Table 2. Basic Characteristics of ICSRs in the JADER Database

Variables	Pemafibrate	Fenofibrate	Bezafibrate
Sex			
Male	19 [67.9]	14 [70.0]	9 [69.2]
Female	9 [32.1]	6 [30.0]	4 [30.8]
Not Specified	0 [0.0]	0 [0.0]	0 [0.0]
Age			
20–50 years	9 [32.1]	4 [20.0]	5 [38.5]

≥60 years	19 [67.9]	16 [80.0]	8 [61.5]
Reporter			
Healthcare Professional	28 [100.0]	19 [95.0]	13 [100.0]
Consumer	0 [0.0]	1 [5.0]	0 [0.0]
Unknown	0 [0.0]	0 [0.0]	0 [0.0]
Year			
2004	–	–	–
2005	–	1 [5.0]	1 [7.7]
2006	–	–	1 [7.7]
2007	–	1 [5.0]	–
2008	–	–	1 [7.7]
2009	–	–	–
2010	–	–	1 [7.7]
2011	–	–	–
2012	–	2 [10.0]	–
2013	–	–	1 [7.7]
2014	–	1 [5.0]	–
2015	–	–	1 [7.7]
2016	–	1 [5.0]	1 [7.7]
2017	–	2 [10.0]	1 [7.7]

2018	–	2 [10.0]	4 [30.8]
2019	6 [21.4]	–	–
2020	2 [7.1]	–	1 [7.7]
2021	7 [25.0]	2 [10.0]	–
2022	5 [17.9]	1 [5.0]	–
2023	3 [10.7]	6 [30.0]	–
2024	5 [17.9]	1 [5.0]	–

This table summarizes the characteristics of ICSRs related to biliary ADEs for each fibrate in the JADER database. Per-drug counts are ICSRs and are not mutually exclusive. The characteristics include patient sex, age, reporter occupation, and year of report. Numbers in parentheses indicate the proportion of reports within each category.

ICSR: individual case safety report; JADER: Japanese Adverse Drug–Event Report; ADEs: adverse drug events.

Table 3. Estimated Weibull Parameters from Time-to-Onset Analysis

PTs	n	β	α	median
cholelithiasis	9	2.05 [1.61–4.76]	485.93 [322.94–630.29]	525.0 [183.0–706.0]
Cholecystitis/ Cholecystitis acute	8	1.29 [0.87–2.94]	447.52 [223.36–705.30]	345.5 [149.0–706.0]
Overall	17	1.59 [1.17–2.56]	469.66 [327.34–613.50]	450.0 [185.0–587.0]

Estimated Weibull parameters and median TTOs for pemafibrate in the JADER dataset (N = 17). This table presents the estimates for each adverse event (cholelithiasis; cholecystitis and cholecystitis acute; all events combined). Values in parentheses indicate 95% CIs (bootstrap).

545 PTs: Preferred Terms; β: shape parameter; α: scale parameter; TTO: time-to-onset; JADER: Japanese
546 Adverse Drug–Event Report; CI: confidence interval.

Figure 1.TIFF

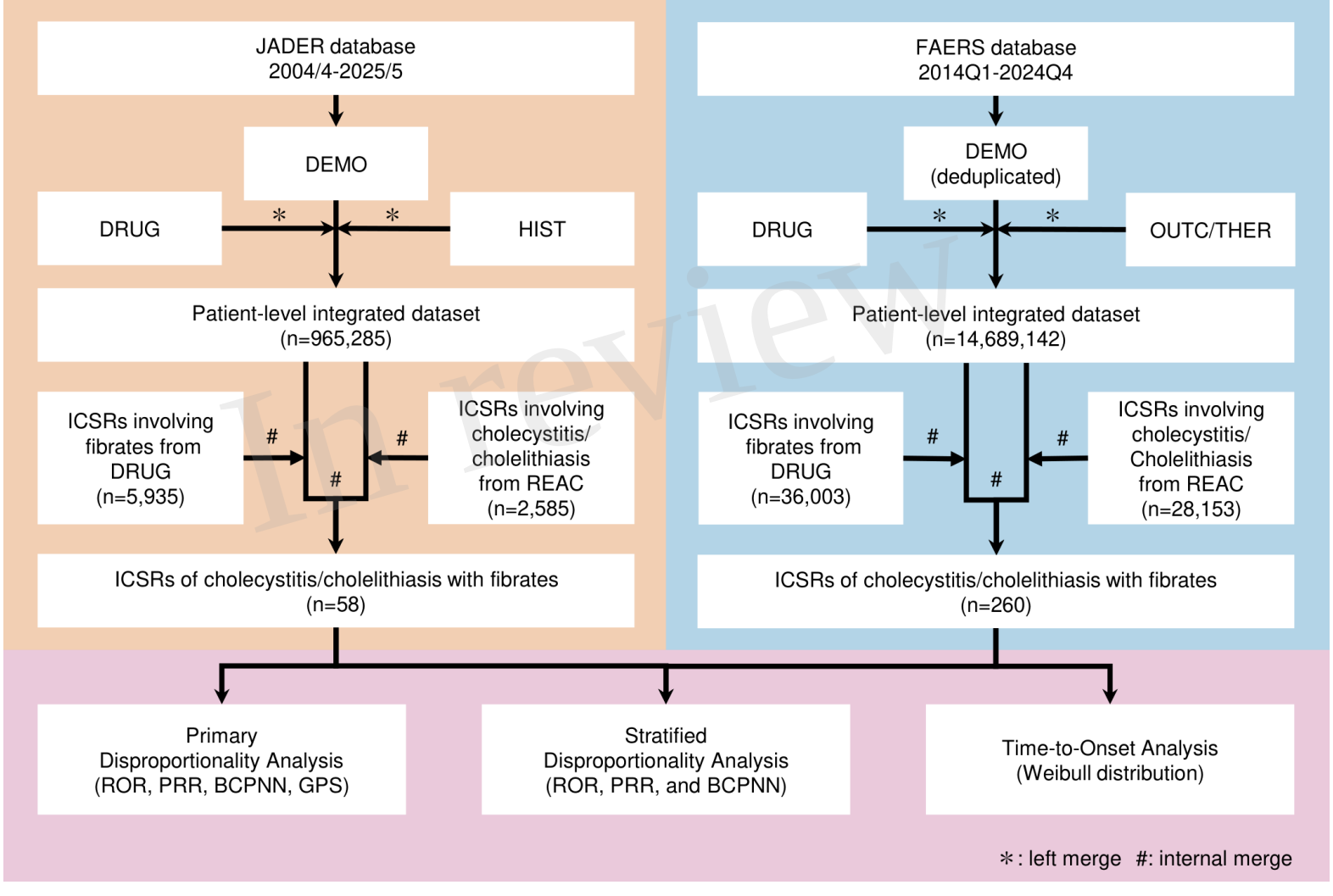


Figure 2.TIF

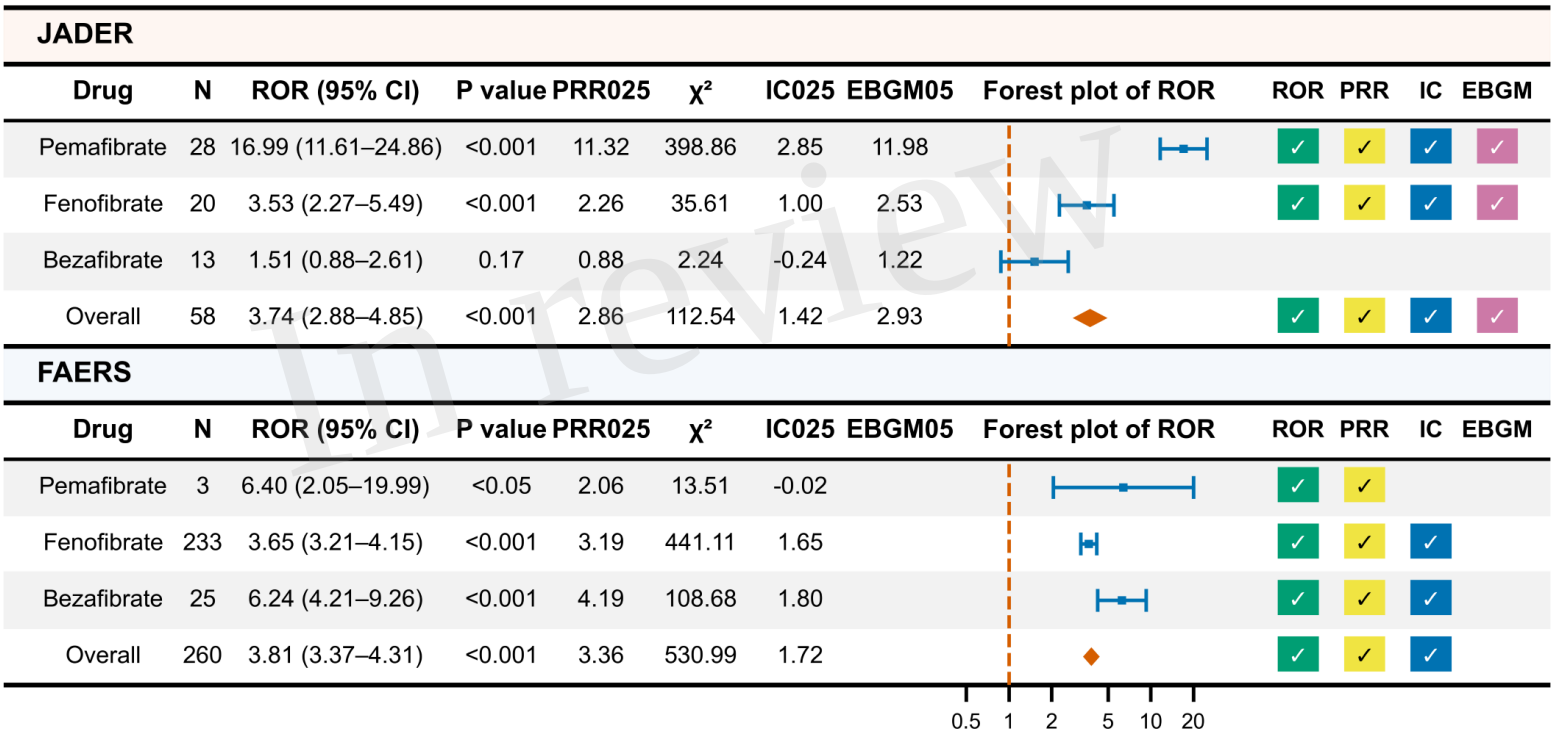
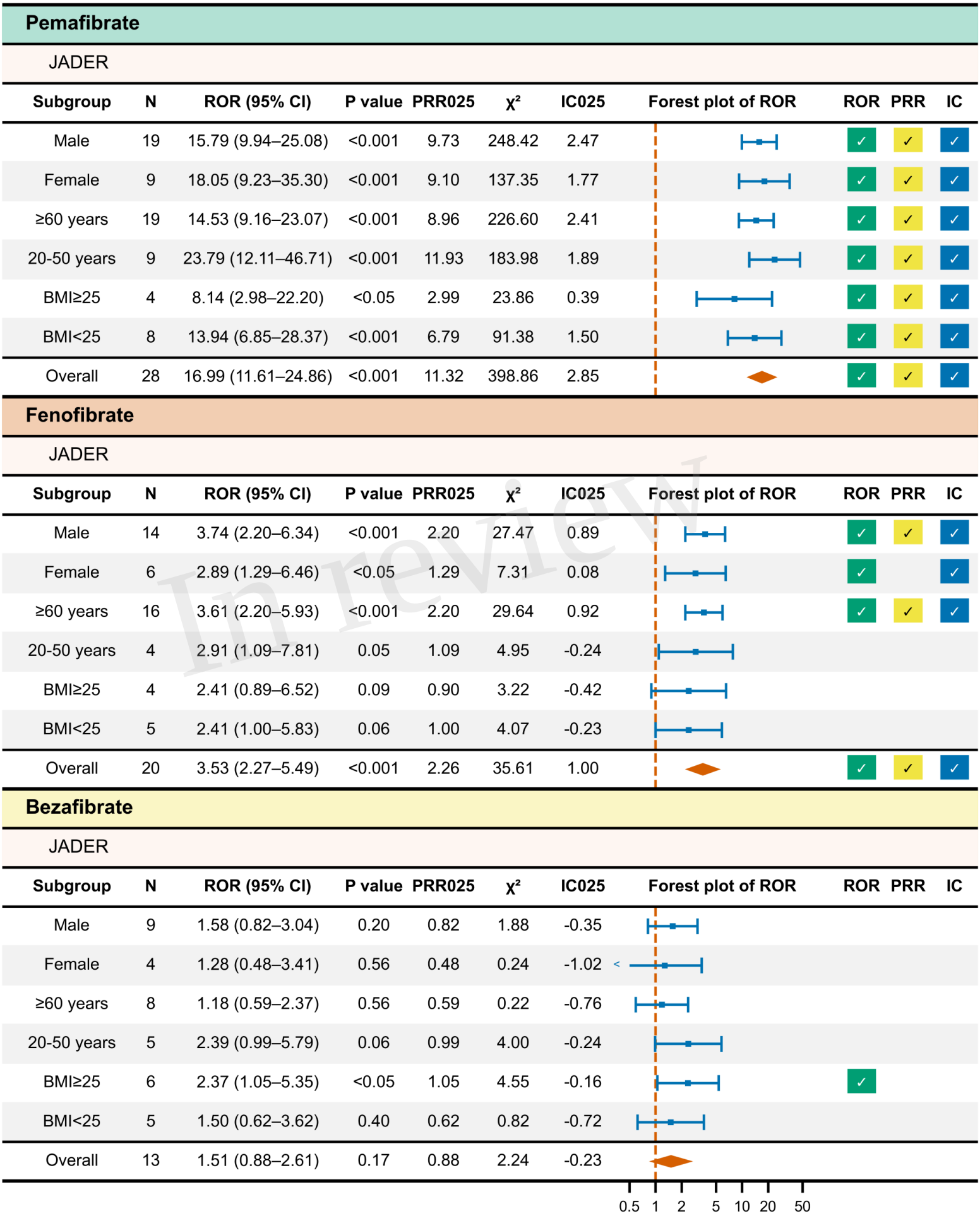


Figure 3.TIF



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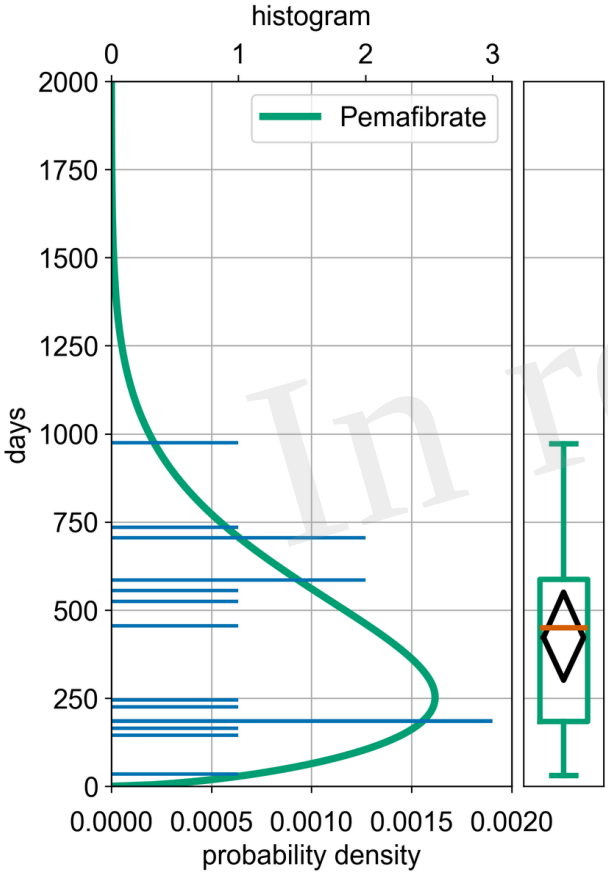

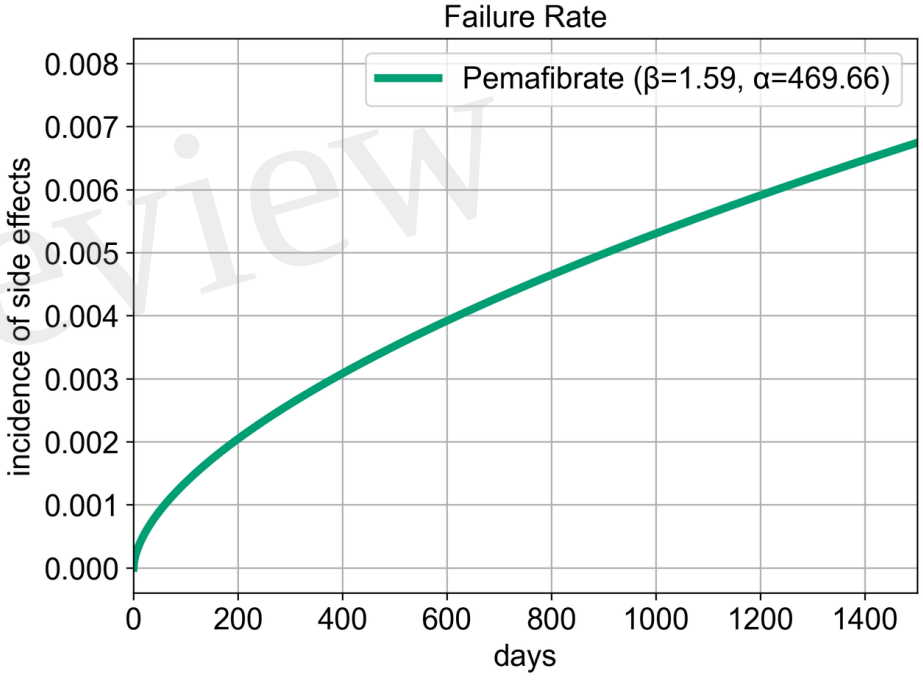

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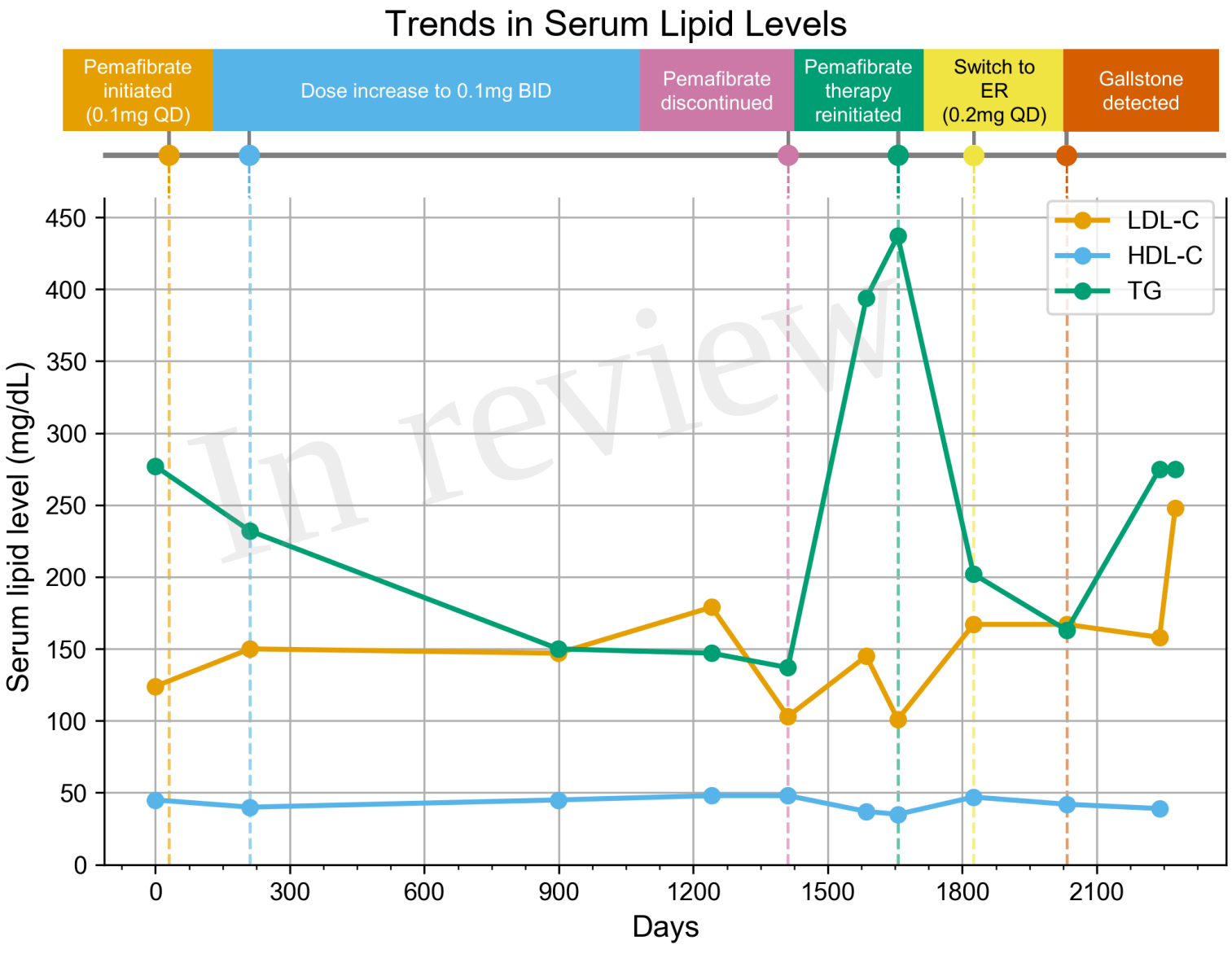
Trends in Serum Lipid Levels
Pemafibrate initiated (0.1mg QD)
Dose increase to 0.1mg BID
Pemafibrate discontinued
Pemafibrate therapy reinitiated
Switch to ER (0.2mg QD)
Gallstone detected
LDL-C
HDL-C
TG
Serum lipid level (mg/dL)
Days
0
50
100
150
200
250
300
350
400
450
0
300
600
900
1200
1500
1800
2100
In review