# AI-Supported Analysis of DILI Phenotypes Reveals Drug-Specific Clinical Patterns While Steatosis Remains Asymptomatic

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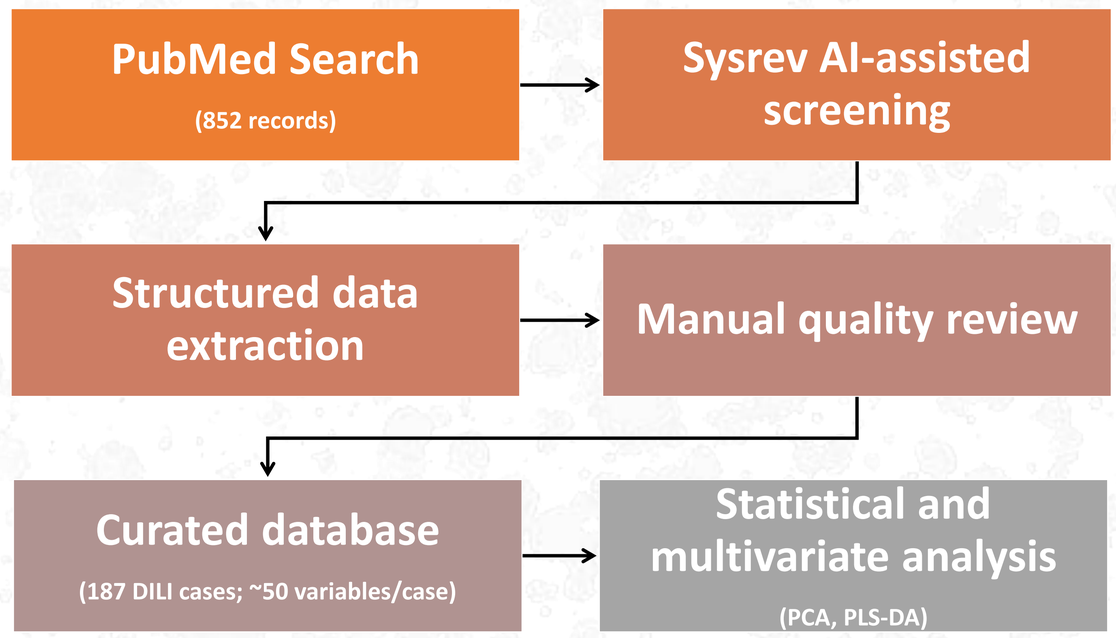
## INTRODUCTION

Drug-induced liver injury (DILI) exhibits marked clinical heterogeneity. Although hepatic steatosis is common in DILI, its impact on disease phenotype and prognosis remains unclear.

We used the AI-supported platform **Sysrev** to systematically analyse published cases of amiodarone, methotrexate and valproate associated DILI and investigate the relative contribution of steatosis and the causative drug to DILI presentation and outcome.

## METHODOLOGY



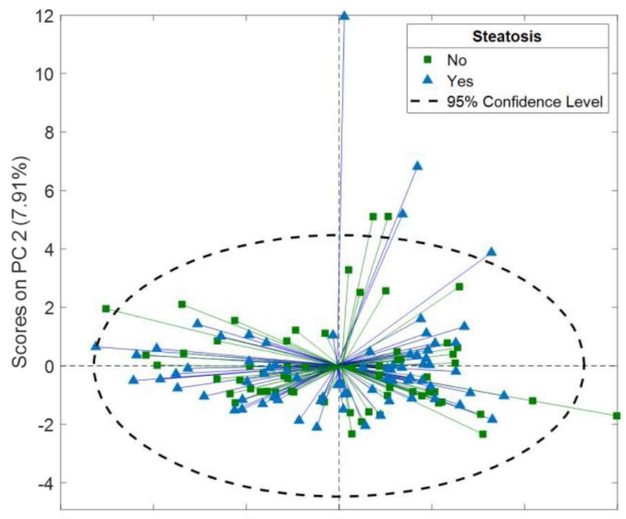

## RESULTS

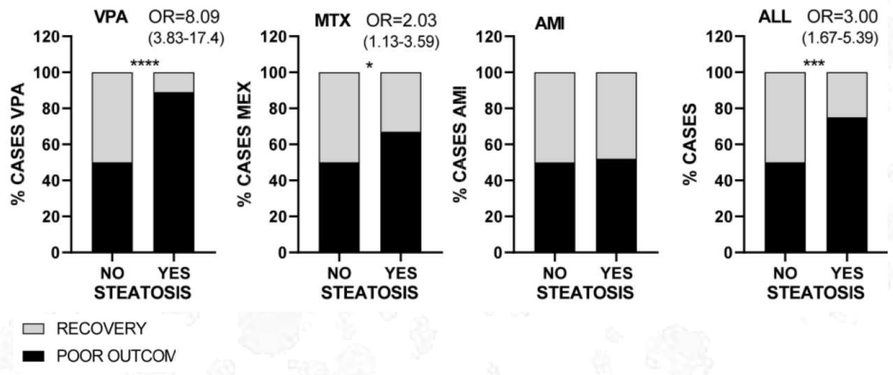
### Liver steatosis does not significantly affect the clinical phenotype of DILI.

Steatosis did not clearly define a distinct DILI phenotype, as steatosis and non-steatosis groups showed largely overlapping clinical, histological, and laboratory profiles, supported by PCA and poor PLS-DA discrimination.

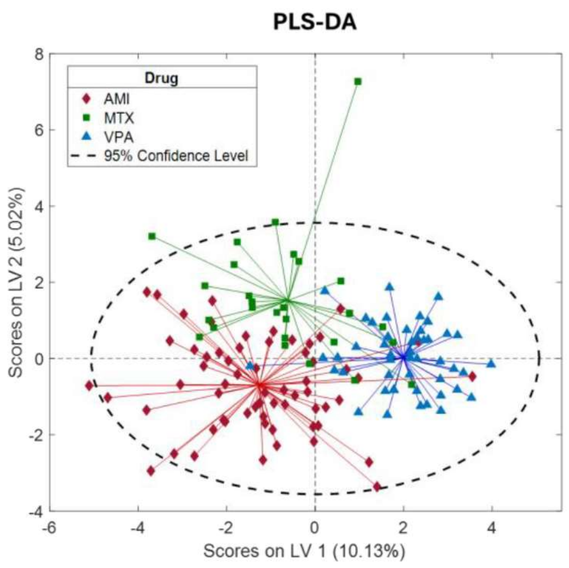
Although steatosis was associated with worse outcomes overall (higher fatality, lower recovery) and more frequent abdominal pain and coagulation abnormalities, these differences were not consistent across drug subgroups (VPA, MTX, AMI).

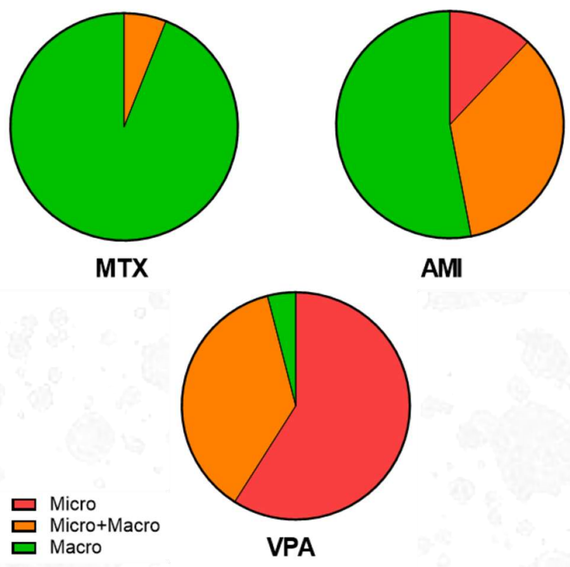
Overall, steatosis alone appears to have limited clinical impact in DILI, with variability mainly driven by drug-specific factors.




| | Fatality | Recovery | Abd. Pain | Coag. Alter. |
|---|---|---|---|---|
| **STEATO** | **60%** | 25% | 23% | 80% |
| **NO STEATO** | 30% | **50%** | 9% | 59% |




### The causative drug impacts significantly the clinical phenotype of DILI

PLS-DA achieved a clear discrimination of drug-specific DILI phenotypes, with stronger classification performance for AMI and VPA than for MTX.

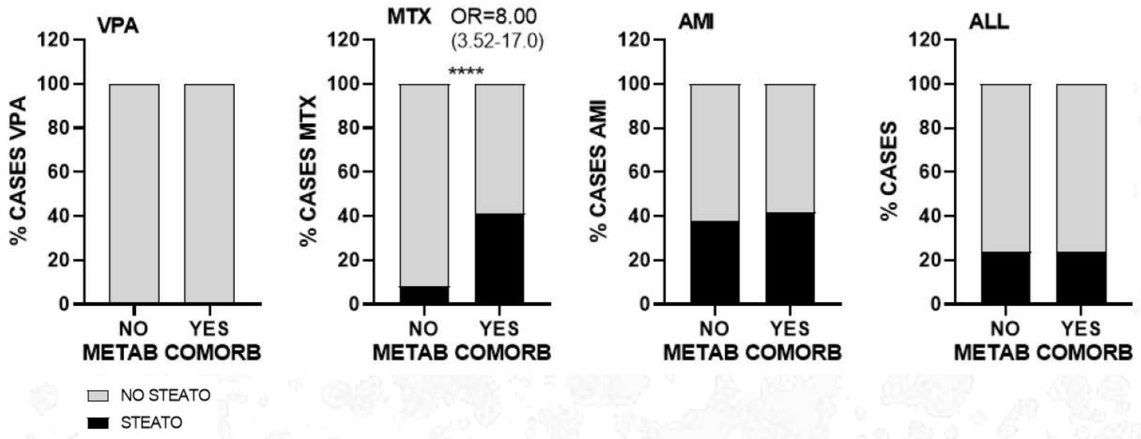
**Key discriminant variables** included Mallory–Denk bodies, inflammation, necrosis, cholestasis, bilirubin, AST, latency and fatality, highlighting **characteristic clinical and histopathological signatures for each drug**.

Steatosis was most frequent in VPA-DILI (81%) vs MTX (52%) and AMI (41%), with distinct patterns: MTX showed mainly macrovesicular steatosis, AMI mixed/macrovesicular, and VPA predominantly microvesicular.

### Contribution of pre-existing steatotic liver disease

Overall, metabolic comorbidities were equally prevalent in steatotic and non-steatotic DILI patients (24% vs. 24%).

However, MTX-related DILI showed a strong association between steatosis and metabolic comorbidities (41% vs. 8%), suggesting underlying MASLD/MetALD in a substantial proportion of cases.




## CONCLUSION

- Steatosis is common in AMI-, MTX- and VPA-associated DILI but does not define a distinct DILI phenotype.
- Steatosis is associated with poorer outcomes, particularly in MTX- and VPA-related DILI.
- Distinct drug-specific phenotypes were identified for AMI, MTX and VPA.
- The causative drug—not steatosis—is the main determinant of DILI phenotype.
- AI-assisted evidence synthesis enabled systematic characterization of DILI phenotypes.

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