Liver chemistries in glycogenic hepatopathy associated with type 1 diabetes mellitus: A systematic review and pooled analysis

Samir Haffar, MD

Annual congress of the Syrian Society of Gastroenterology

30 August – 1 September 2023, Dama Rose Hotel, Damascus, Syrian Arab Republic

Received: 10 January 2021 | Revised: 7 February 2021 | Accepted: 8 February 2021

DOI: 10.1111/liv.14827

ORIGINAL ARTICLE

Liver INTERNATIONAL WILEY

Liver chemistries in glycogenic hepatopathy associated with type 1 diabetes mellitus: A systematic review and pooled analysis

Samir Haffar[1] | Manhal Izzy[2] | Hany Habib[3] | Takaaki Sugihara[4] | Darrick K. Li[5] | Ayush Sharma[6] | Zhen Wang[7] | M. Hassan Murad[7] | Kymberly D. Watt[6] | Fateh Bazerbachi[8]

Glycogenic hepatopathy

- First described in 1930 by Mauriac in children with poorly controlled T1DM, hepatomegaly, delay in growth/puberty & cushingoid features
- Can occur without full spectrum of Mauriac syndrome: hepatomegaly & perturbations of liver chemistries
- Diagnosis made after ruling out a wide range liver disease
- Liver biopsy is the gold standard for diagnosis
- Liver chemistries in GH may vary & their patterns not well elucidated

Objective of the systematic review

Perform a systematic review of T1DM and biopsy-proven glycogenic hepatopathy reports to identify characteristic patterns of liver chemistries abnormalities

Inclusion criteria

Patients with T1DM and biopsy-proven GH without other clinical manifestations of Mauriac Syndrome

Exclusion criteria

- Duplicated studies
- Studies with insufficient data
- T1DM & GH not confirmed by liver biopsy
- TIDM & GH with clinical Mauriac syndrome
- TIDM & GH associated with other liver diseases
- GH without T1DM: T2DM, urea cycle defects, dumping syndrome, anorexia nervosa, high-dose steroid therapy

Haffar S et al. Liver International 2021;41:1545–1555.

Normal values of liver chemistries

Liver chemistries	Normal values	References
ALT	F: ≤ 25 U/L, M: ≤ 33U/L	ACG guidelines [1]
AST	≤ 40 U/L	Livertox [2]
Total bilirubin	≤ 1.2 mg/dL, 20 μmol/L	Livertox [2]
Alkaline phosphatase	≤ 115 U/L	Livertox [2]
GGT	≤ 50 U/L	Livertox [2]
PT	≤ 12.5 sec or ≥ 85%	Pagana et al. [3]
INR	≤ 1.1	Pagana et al. [3]
Albumin	≥ 35 g/L	

1. Kwo PY et al. Am J Gastroenterol. 2017;112(1):18 – 35.
2. LiverTox: https://www.ncbi.nlm.nih.gov/books/ NBK54 7852/.
3. Pagana KD et al. Mosby's Diagnostic & Laboratory Test Reference. 14th ed. St. Louis, MO: Elseiver; 2019.

Magnitude of total bilirubin, ALP & GGT elevations

- Calculated by multiple of the ULN
- ALP evaluated only in adults ≥ 18 years because it is higher in children than in adults, and because the normal range varies with age in children

ALP: alkaline phosphatase – GGT: gamma glutamine transferase

Magnitude of ALT and AST elevations

Classified according to the ACG clinical guidelines for the evaluation of abnormal liver chemistries:

- **Borderline** $< 2 \times$ ULN
- **Mild** $2 – 5 \times$ ULN
- **Moderate** $5 – 15 \times$ ULN
- **Severe** $> 15 \times$ ULN
- **Massive** $> 10\,000$ U/L

ULN: upper limit of normal

Kwo PY ET AL. ACG clinical guideline: evaluation of abnormal liver chemistries. Am J Gastroenterol 2017;112(1):18–35.

AST-to- ALT ratio

Calculated by dividing the AST value by the ALT value in case of abnormal results of either or both transaminases

R ratio

- **Formula:**

  (ALT value/ALT ULN) ÷ (ALP value/ALP ULN)

- **Interpretation:**

< 2	Cholestatic injury
2 – 5	Mixed pattern of hepatic injury
> 5	Hepatocellular injury

ALT: alanine aminotransferase – ALP: alkaline phosphatase – ULN: upper limit of normal

Chalasani NP et al. Am J Gastroenterol 2014;109(7):950-966.

Statistical analyses

- Continuous variables: **Median & IQR**
- Dichotomized variables: **Percentage**
- Correlation of abnormal ALT & AST: **Pearson coefficient**
- Correlation of R based on ALT & AST: **Pearson coefficient**
- A two-sided **$p < 0.05$** was considered statistically significant
- Statistical analyses were conducted using **Stata version 16**

Haffar S et al. Liver International 2021;41:1545–1555.

Two subgroup analyses

- Comparison the magnitude of ALT & AST elevation, AST-to-ALT ratio, and ALT-based R ratio in the five subgroups: adults vs children, males vs females, patients admitted for DKA vs those without, presence vs absence of ANA, & presence vs absence of liver fibrosis
- Stratification of transaminase elevation into 3 groups:
  Up to 299 U/L, 300-999 U/L, and ≥1000 U/L
  Clarify GH cases with transaminases elevation in range of NAFLD (usually up to 300) or range of acute viral hepatitides (usually ≥1000)

Haffar S et al. Liver International 2021;41:1545–1555.

Murad tool for evaluating methodological quality of case reports and case series

Domains	Leading explanatory questions
Selection	Does the patient(s) represent(s) the entire experience of the investigator (center)?
Ascertainment	1. Was the exposure sufficiently ascertained? 2. Was the outcome sufficiently ascertained?
Causality	Were other plausible causes that may explain the observation ruled out?
Reporting	Is the case(s) relayed with adequate details to allow other investigators to replicate the research?

Murad MH et al. Methodological quality & synthesis of case series & case reports. Evid Based Med 2018;23:60–3.

The PRISMA statement

checklist with 27 items

Systematic review reported in line with the guidelines of the **P**referred **R**eporting **I**tems for **S**ystematic reviews and **M**eta-**A**nalyses (**PRISMA**) with an *a priori* study protocol

Moher D et al. PLoS Medicine. 2009;6(7):e1000097.

Literature search

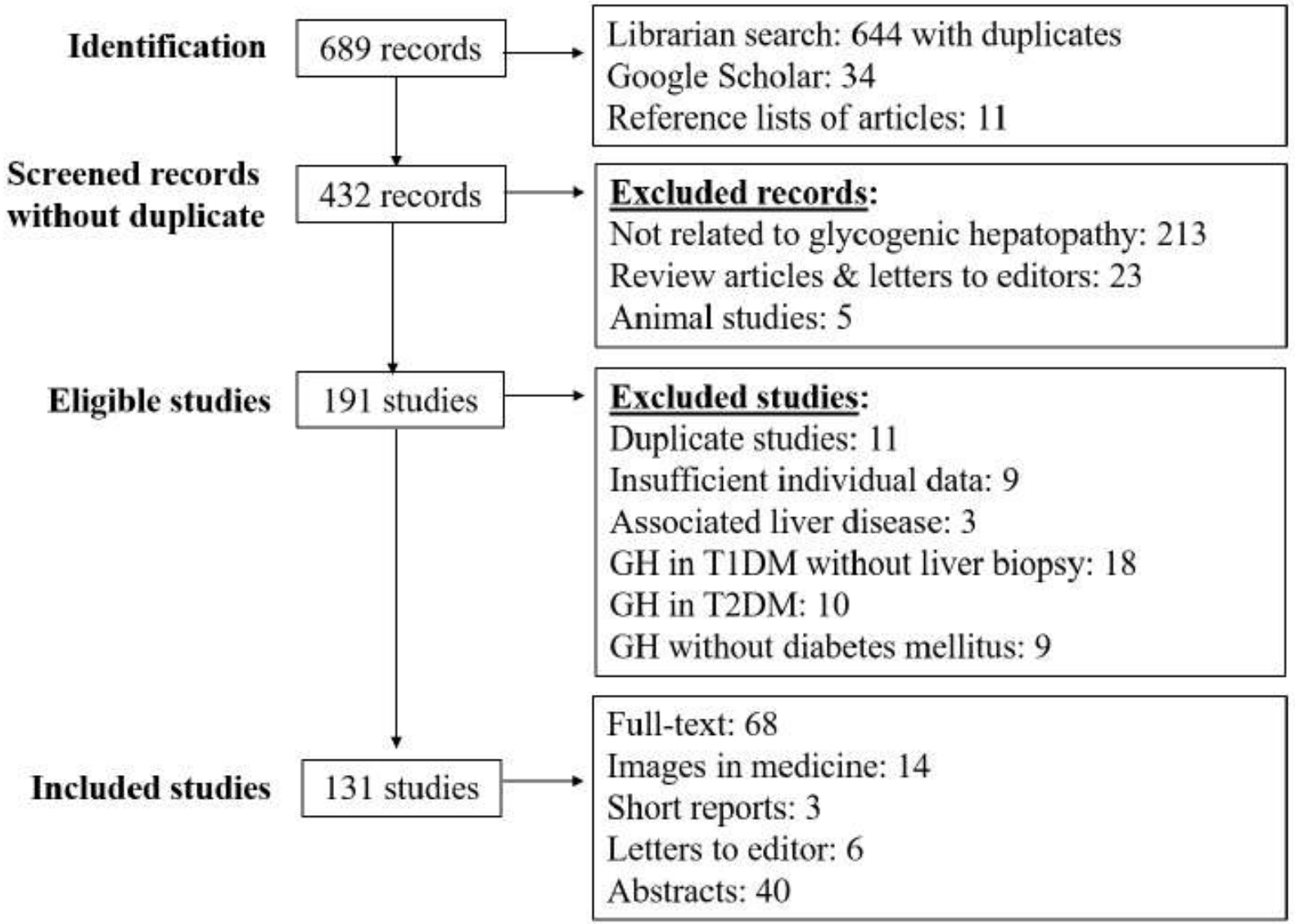
- Language-unrestricted search of **several databases** conducted by experienced librarian: Embase, Ovid Healthstar, Ovid MEDLINE(R), Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) Daily, EBM Reviews –Cochrane Central Register of Controlled Trials, EBM Reviews, & Cochrane Database of Systematic Reviews

- **Google Scholar database**: first 300 entries using the terms "glycogenic hepatopathy"

- **Reference lists of relevant papers:** screened manually

Haffar S et al. Liver International 2021;41:1545–1555.

Flow diagram through the different phases of the systematic review



Haffar S et al. Liver International 2021;41:1545–1555.

Results -1

Characteristics	No of patients with reported results	Results
Demographic characteristics:		
- Age at diagnosis, years, median (IQR)	191	20 (8)
- Adults (≥ 18 years), %	192	141 (73%)
- Females, %	191	126 (66%)
- Ethnicity: Caucasians, Asians & Arabs, %	170	74%, 18% and 3%
Other characteristics:		
- Presence of autoimmune diseases, %	176	14 (8%)
-T1DM duration before dg, years, median (IQR)	129	10 (9)
- Presence of diabetic complications, %	145	18 (12%)
- Single or multiple episodes of DKA, %	156	109 (70%)
- Single or multiple episodes of hypoglycemia, %	128	20 (16%)
- BMI at presentation in adults, kg/m^2, median (IQR)	56 of 141 adults	21.05 (3.45)
Symptoms:		
- Abdominal pain, %	187	113 (60%)
- Nausea and/or vomiting, %	186	79 (42%)
- Patients admitted for DKA, %	165	56 (34%)

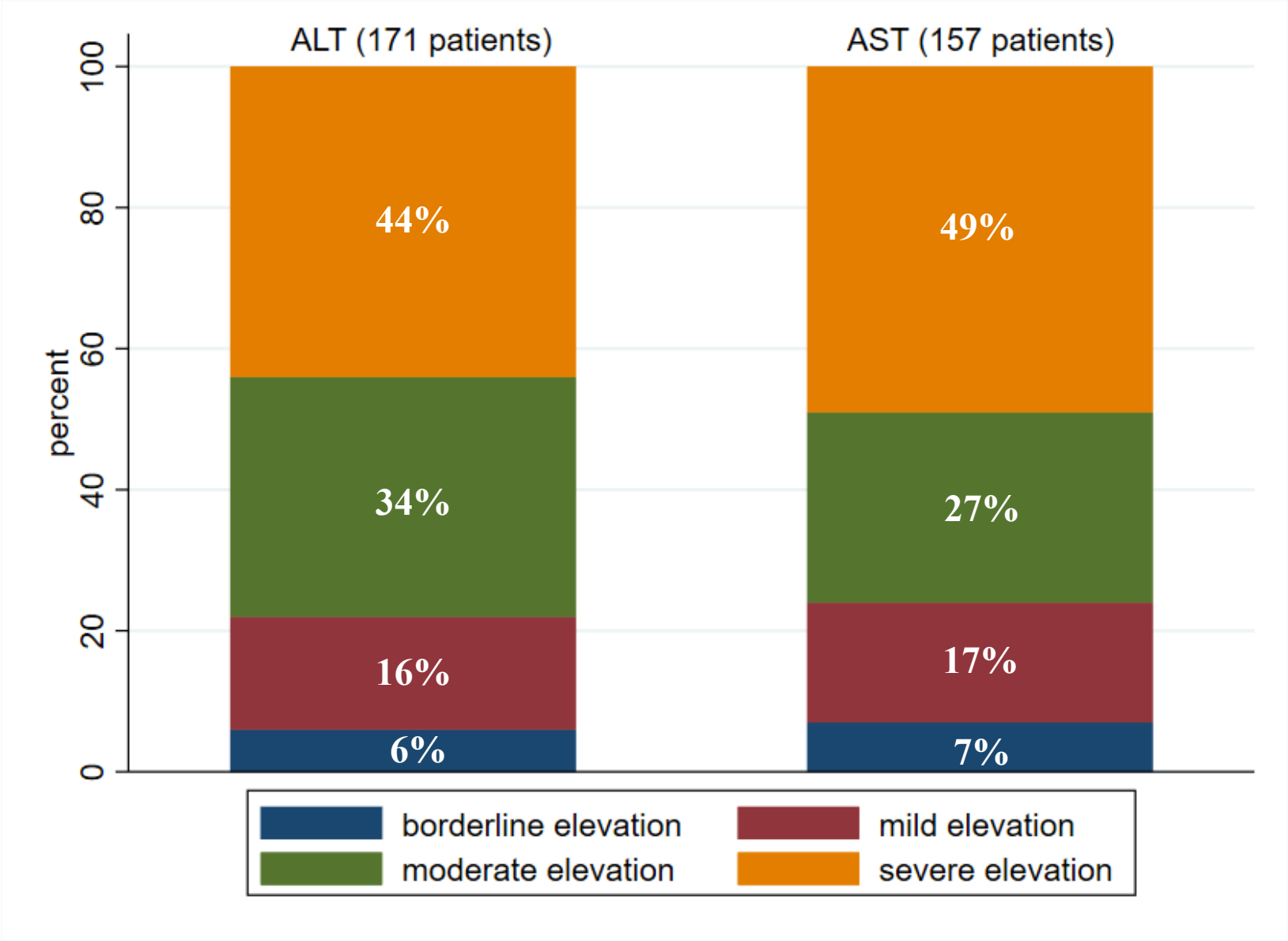
Results - 2

Characteristics	No of patients with reported results	Results
Clinical examination and imaging studies:		
- Hepatomegaly clinically or on imaging, %	185	176 (95%)
- Splenomegaly clinically or on imaging, %	162	3 (2%)
- Ascites clinically or on imaging, %	179	9 (5%)
- Edema, %	172	11 (6%)
Laboratory exams:		
- FBG at presentation, mg/dL, median (IQR)	60	402.5 (271.25)
- HbA1c at presentation, median (IQR)	142	12% (2.7)
Liver biopsy:		
- No staining, %	67	67/192 (35%)
- PAS or best carmine alone, %	46	46/192 (24%)
- PAS/best carmine & diastase/amylase, %	79	79/192 (41%)
- Fibrosis on liver biopsy, %	192	14 (7%)

IQR: interquartile range

Haffar S et al. Liver International 2021;41:1545–1555.

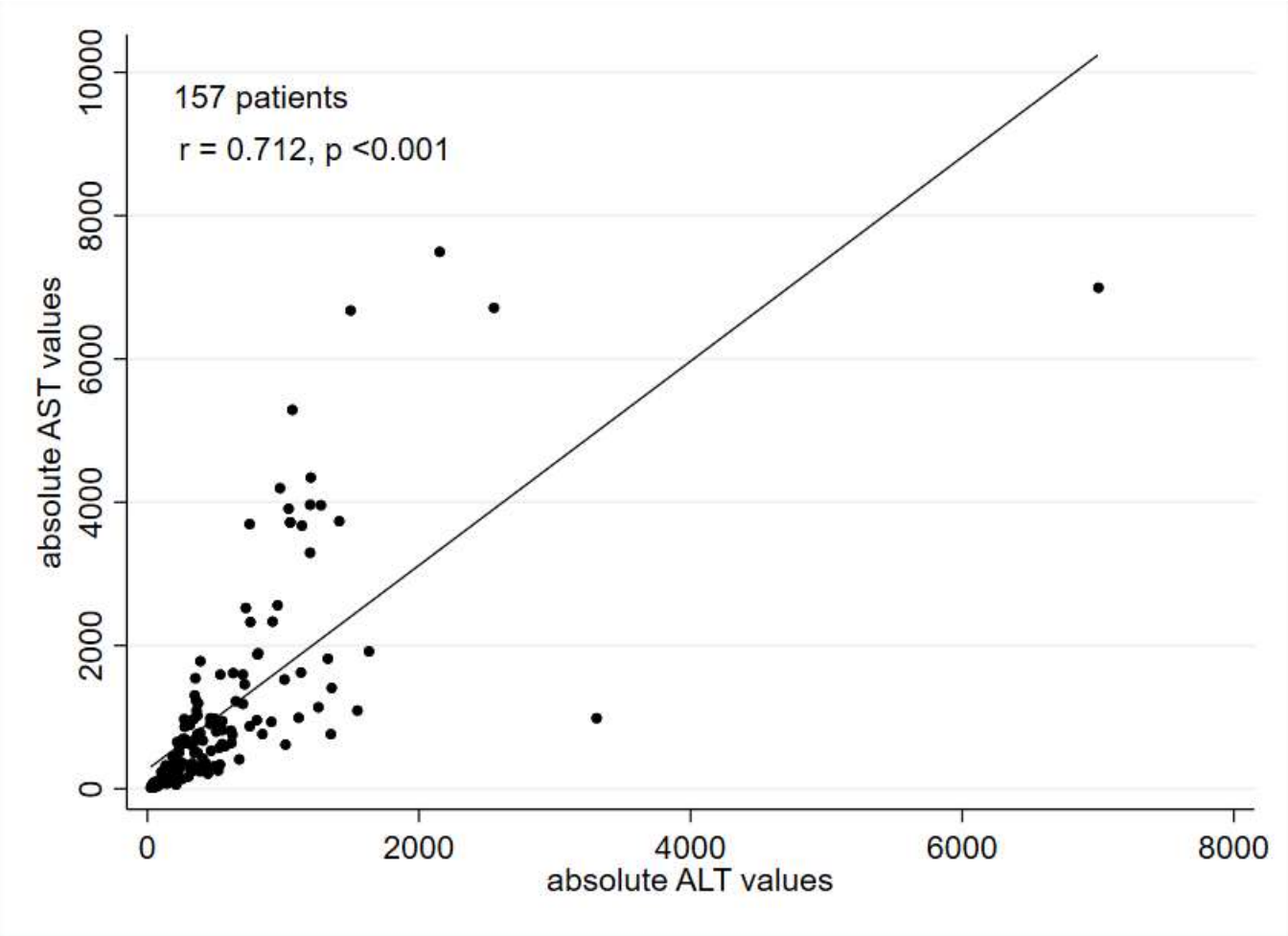
Magnitude of ALT & AST elevation (ACG criteria)



Haffar S et al. Liver International 2021;41:1545–1555.

Correlation between ALT and AST values

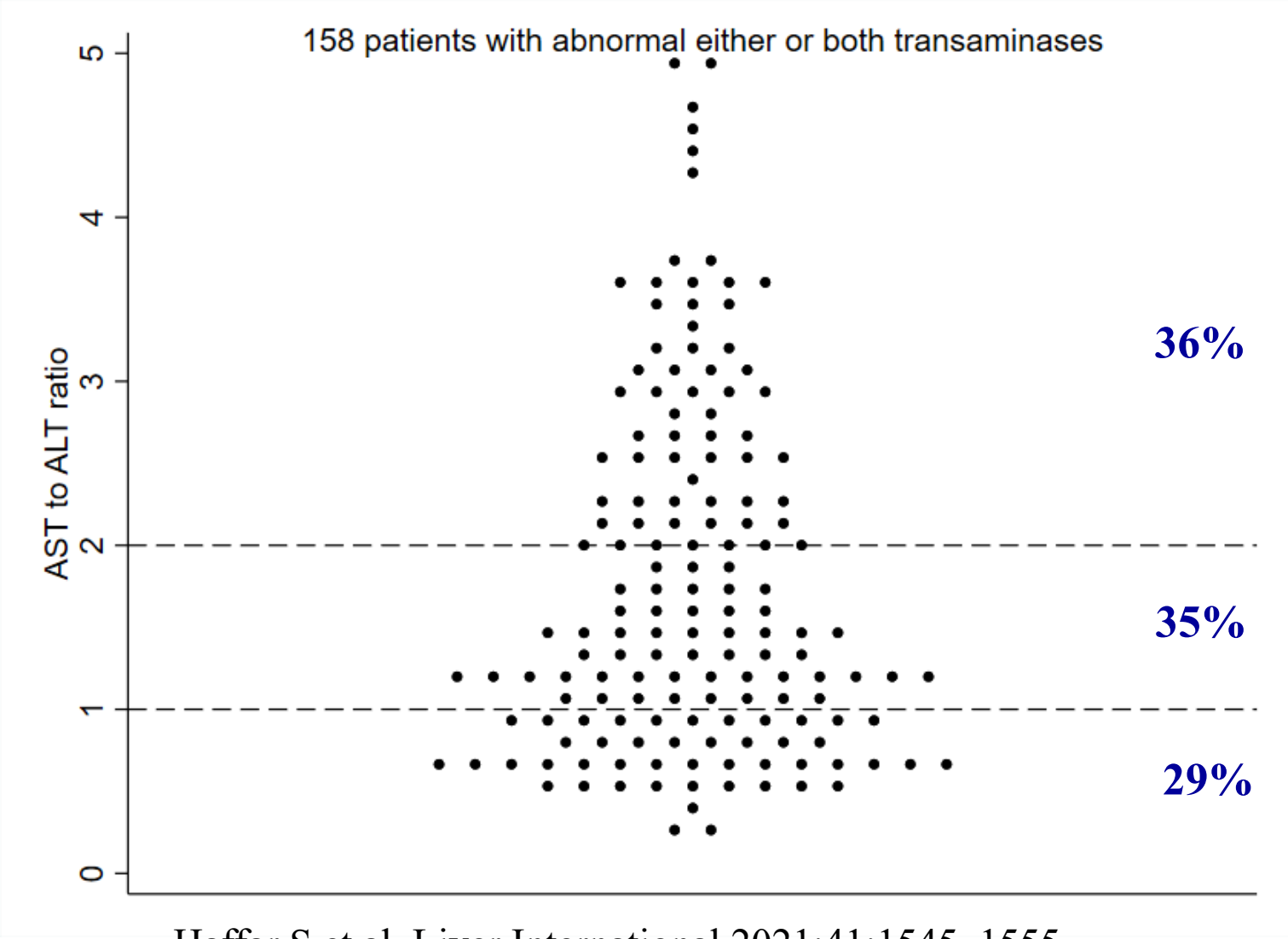
Pearson correlation coefficient (r)



Haffar S et al. Liver International 2021;41:1545–1555.

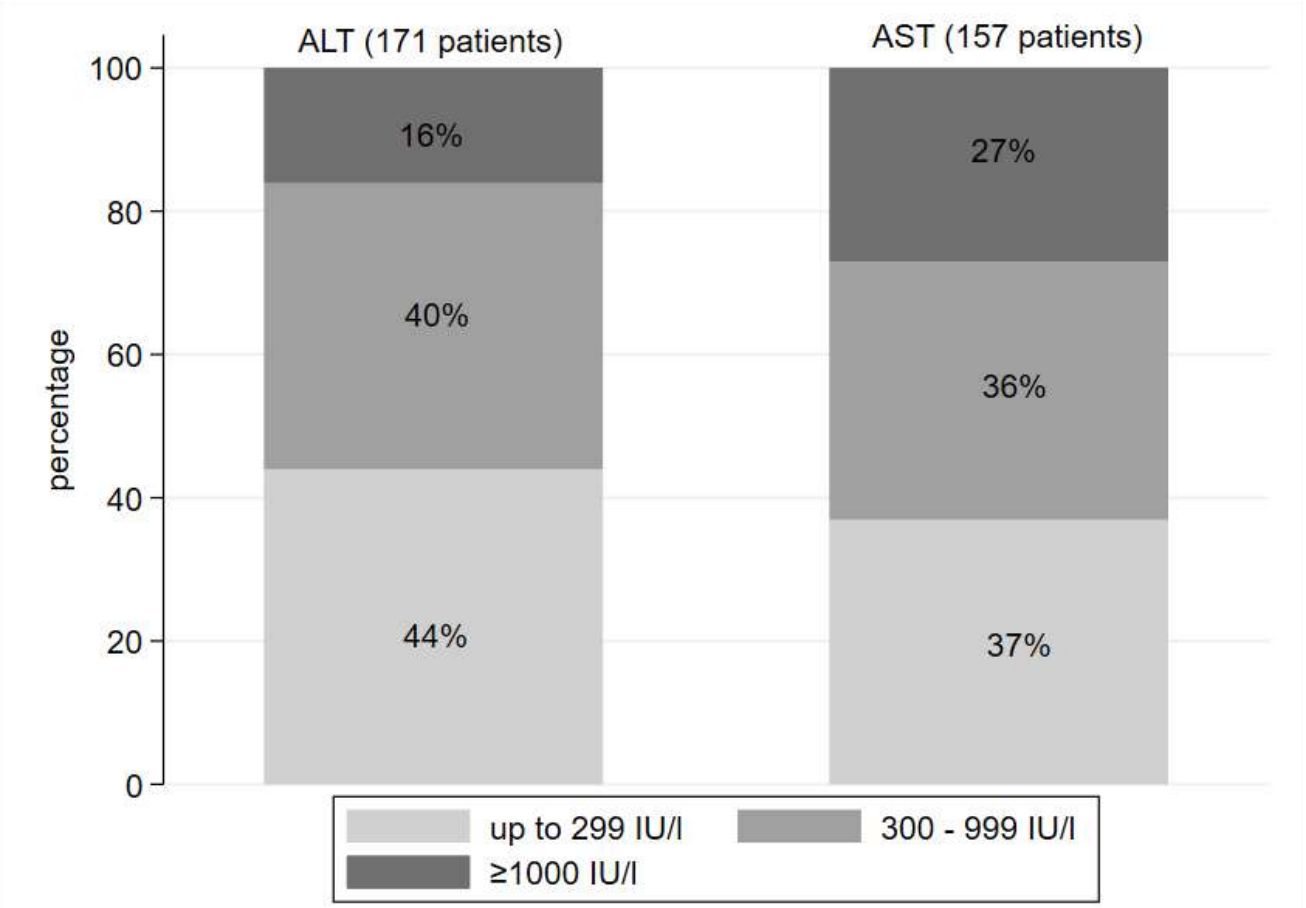
AST to ALT ratio

AST-to-ALT ratio > 1 in **71% of patients**



Haffar S et al. Liver International 2021;41:1545–1555.

Stratification of transaminases into 3 subgroups

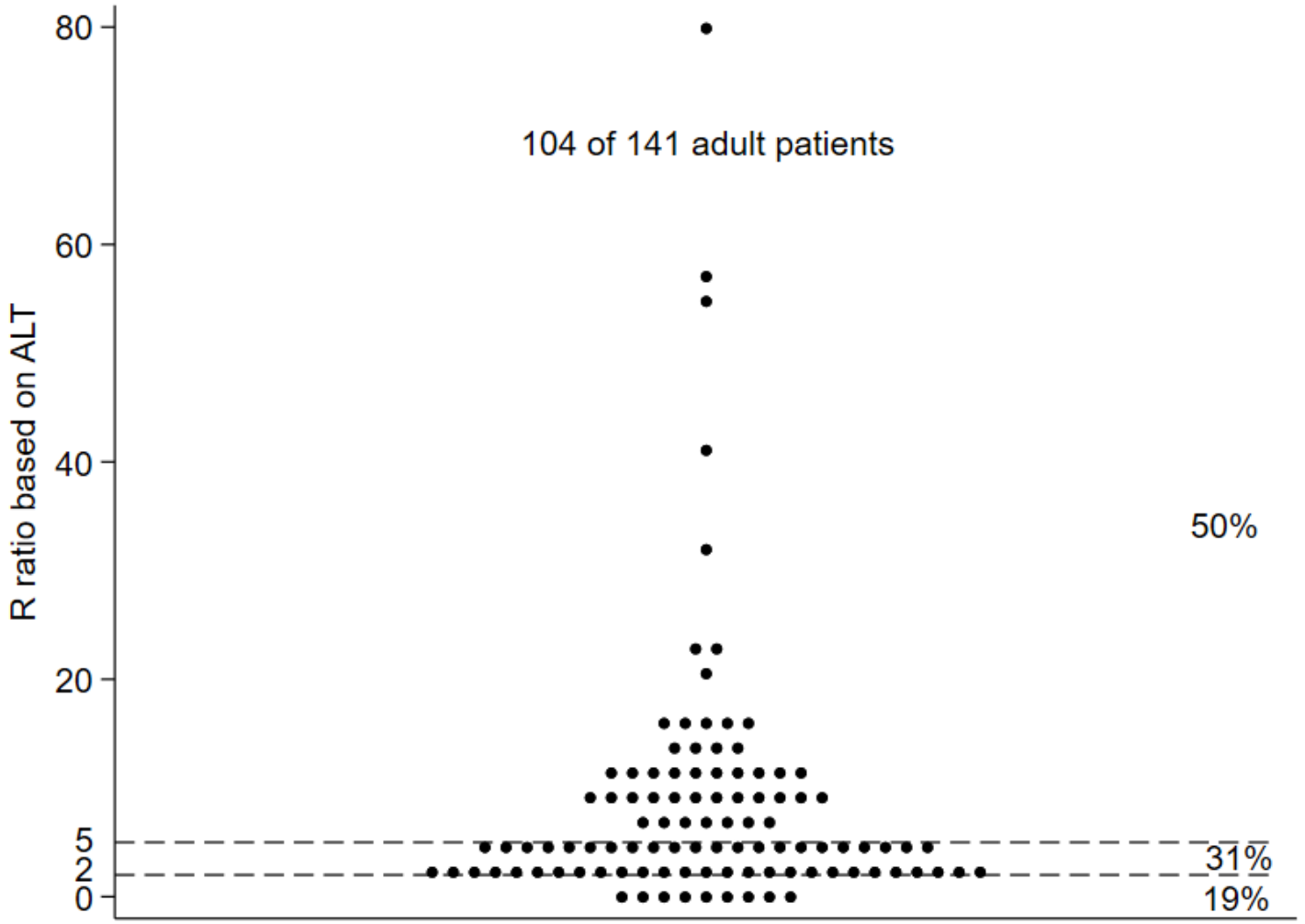


Transaminase elevation exceeded threshold observed in NAFLD or in alcohol-associated liver disease in approximately 60% of patients

Haffar S et al. Liver International 2021;41:1545–1555.

R ratio based on ALT

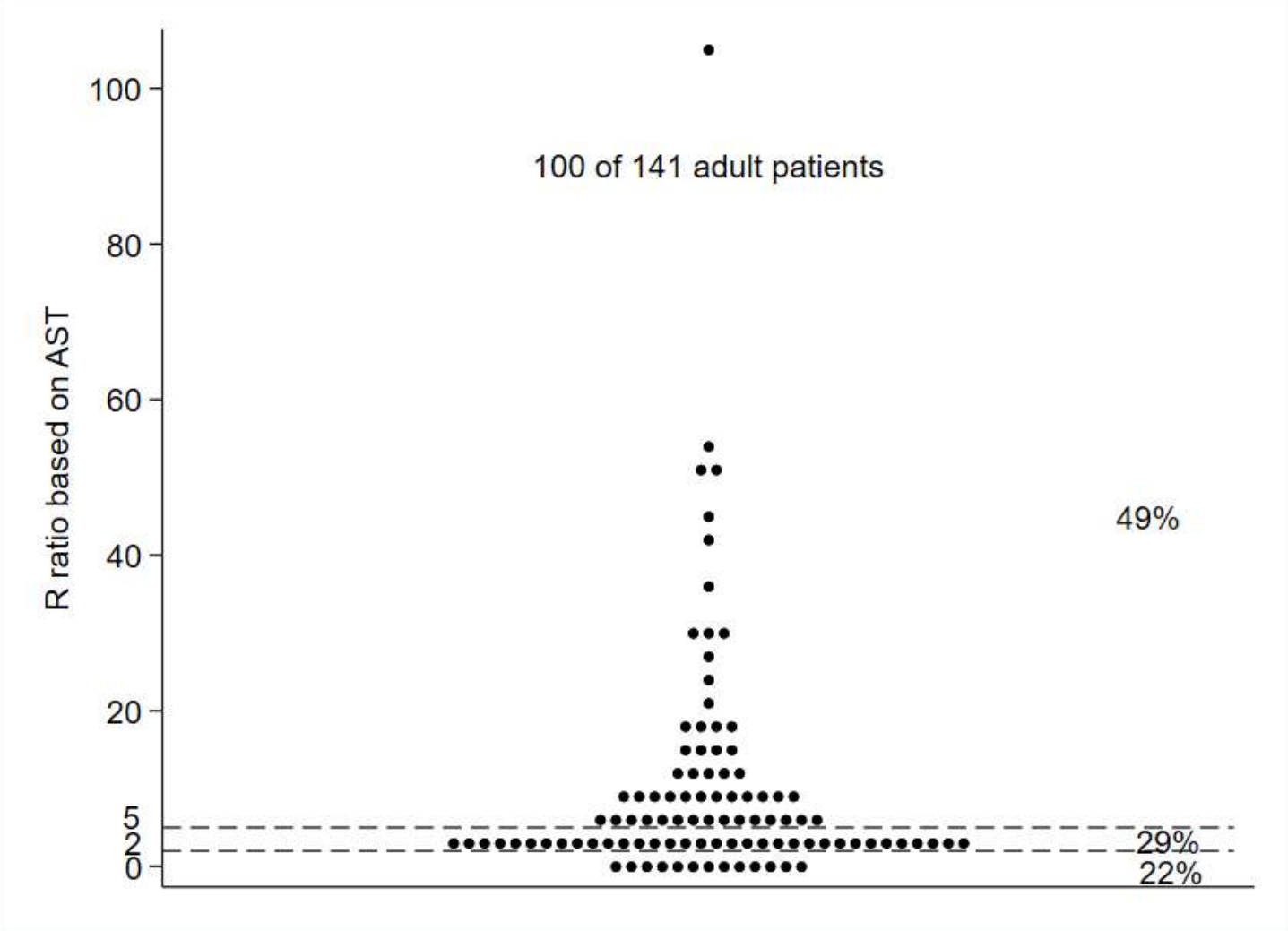
Hepatocellular to mixed pattern of hepatic injury in **81% of patients**



Haffar S et al. Liver International 2021;41:1545–1555.

R ratio based on AST

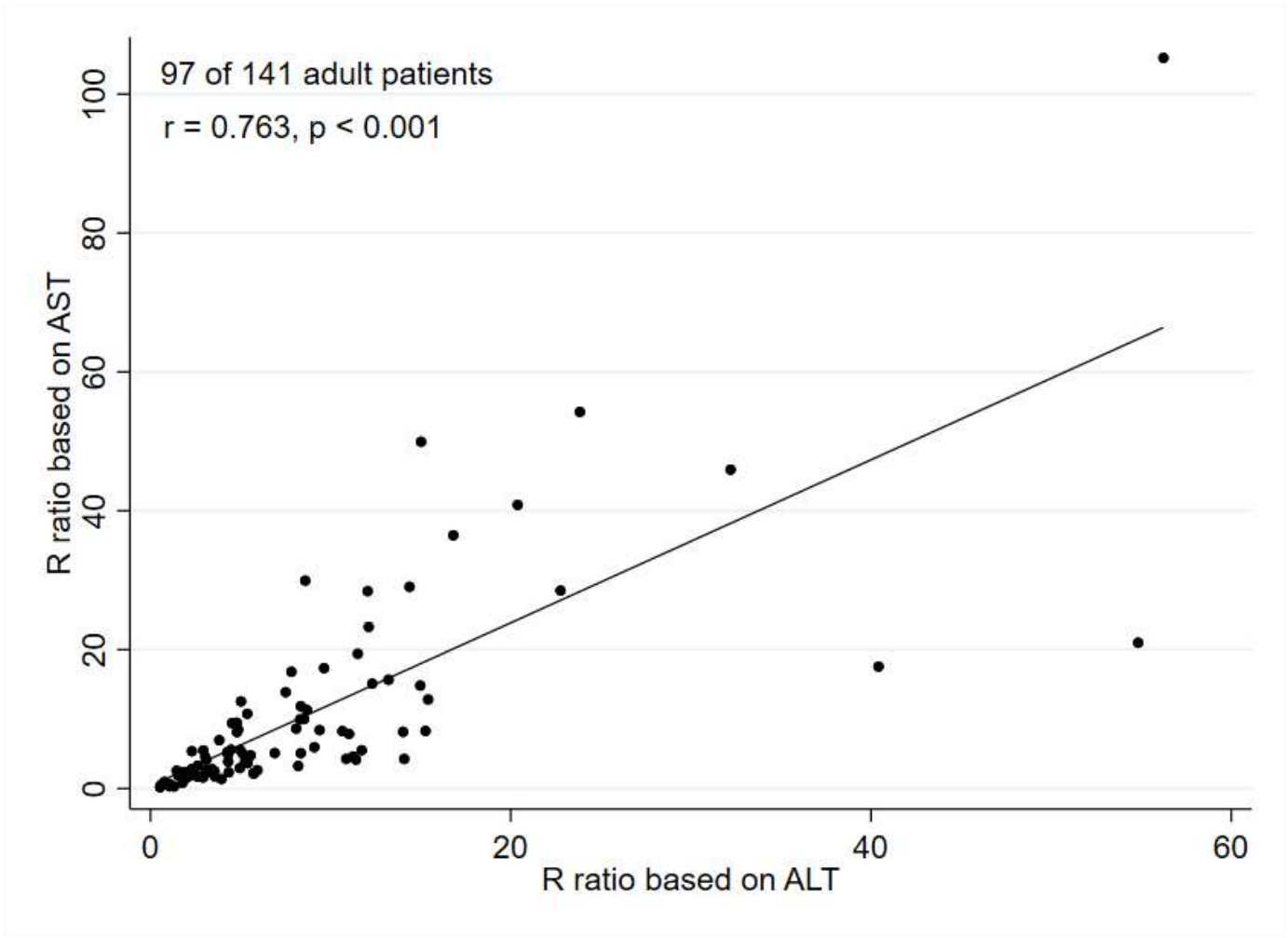
Hepatocellular to mixed pattern of hepatic injury in **78% of patients**



Haffar S et al. Liver International 2021;41:1545–1555.

Correlation between ALT-R ratio & AST-R ratio

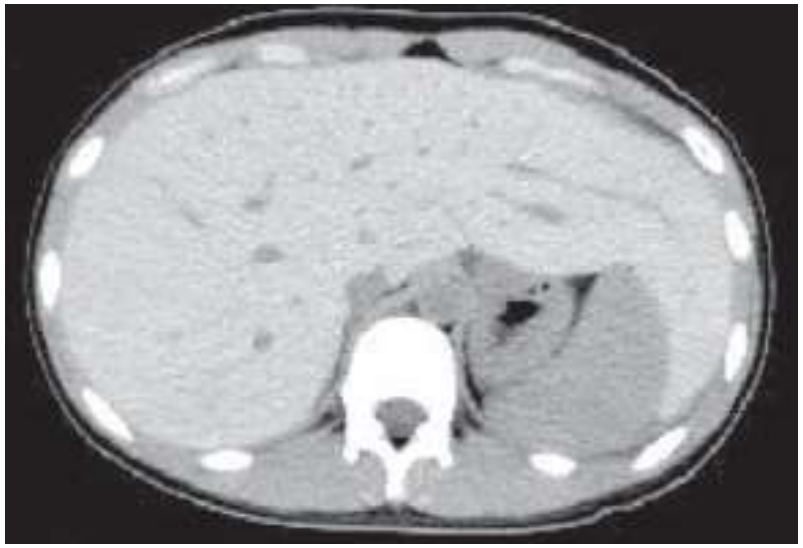
Pearson correlation coefficient (r)



Haffar S et al. Liver International 2021;41:1545–1555.

Unenhanced computed tomography

Glycogenic hepatopathy



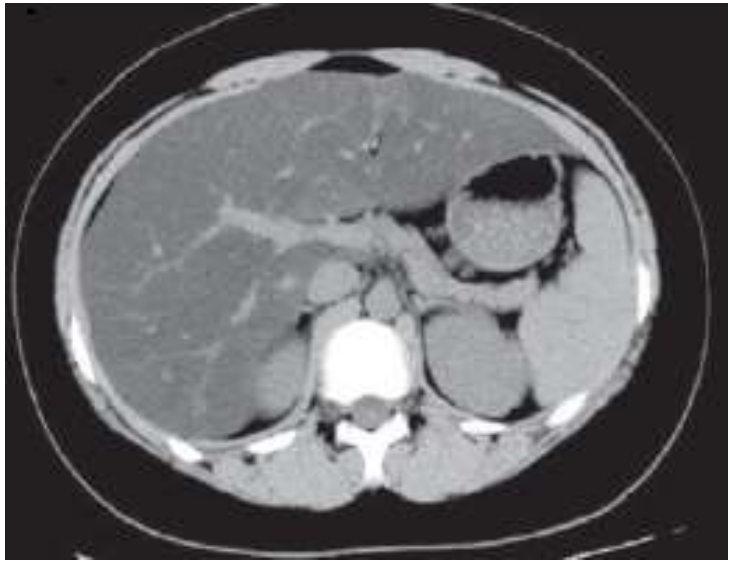
High density liver

ΔΔ: iodine in amiodarone use

iron overload in hemochromatosis

13 out of 60 patients with reported CT

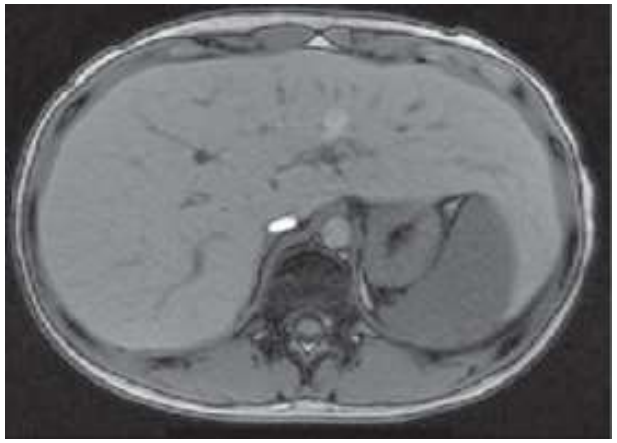
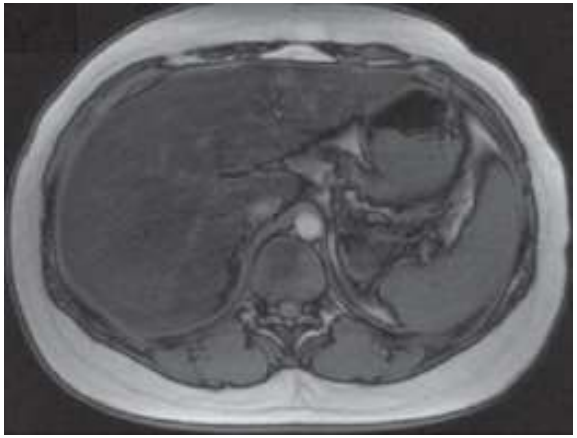
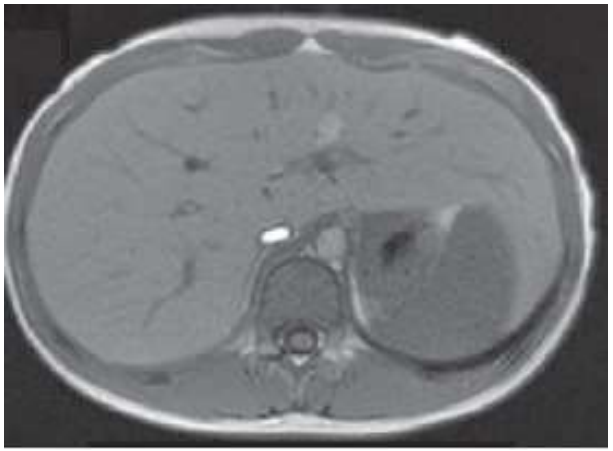
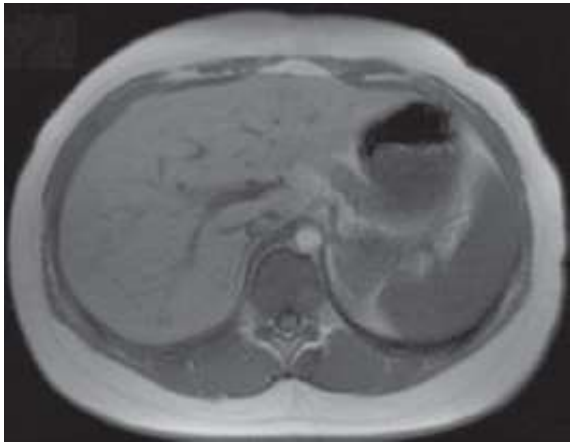
NAFLD



Low density liver

Saikusa M et al. Pediatrics International (2013) 55, 806–807.

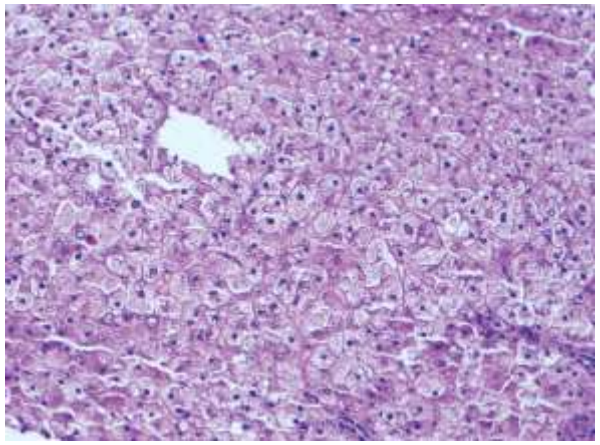
Gradient dual-echo MRI

	Glycogenic hepatopathy	NAFLD
in-phase image		
out-of-phase image		
	iso-intense of the 2 phases 1 of 12 patients with reported MRI	in-phase: low intensity out-of-phase: high intensity

Saikusa M et al. Pediatrics International (2013) 55, 806–807.

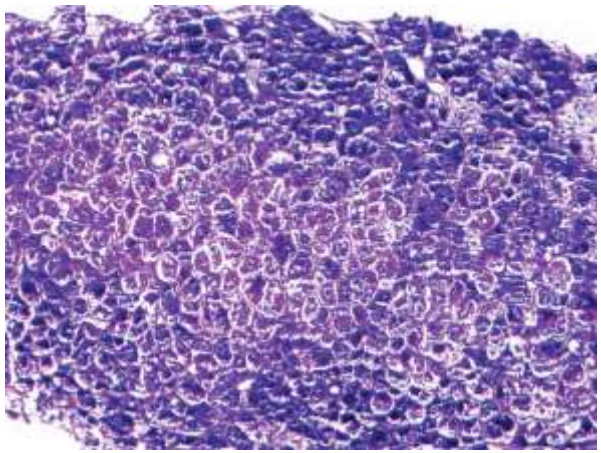
Hematoxylin & eosin

Preserved parenchymal architecture and enlarged pale hepatocytes



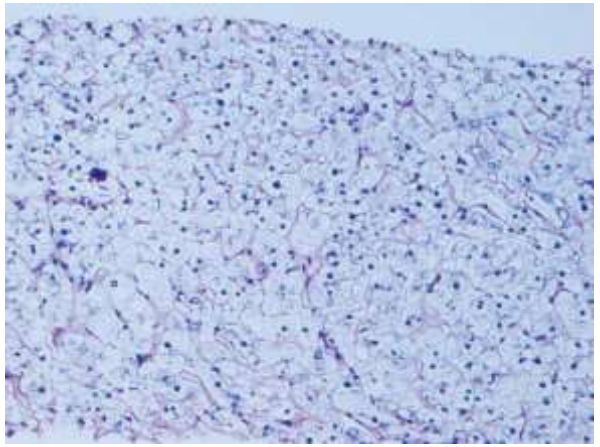
PAS staining

Abundant cytoplasmic glycogen deposits demonstrated by PAS



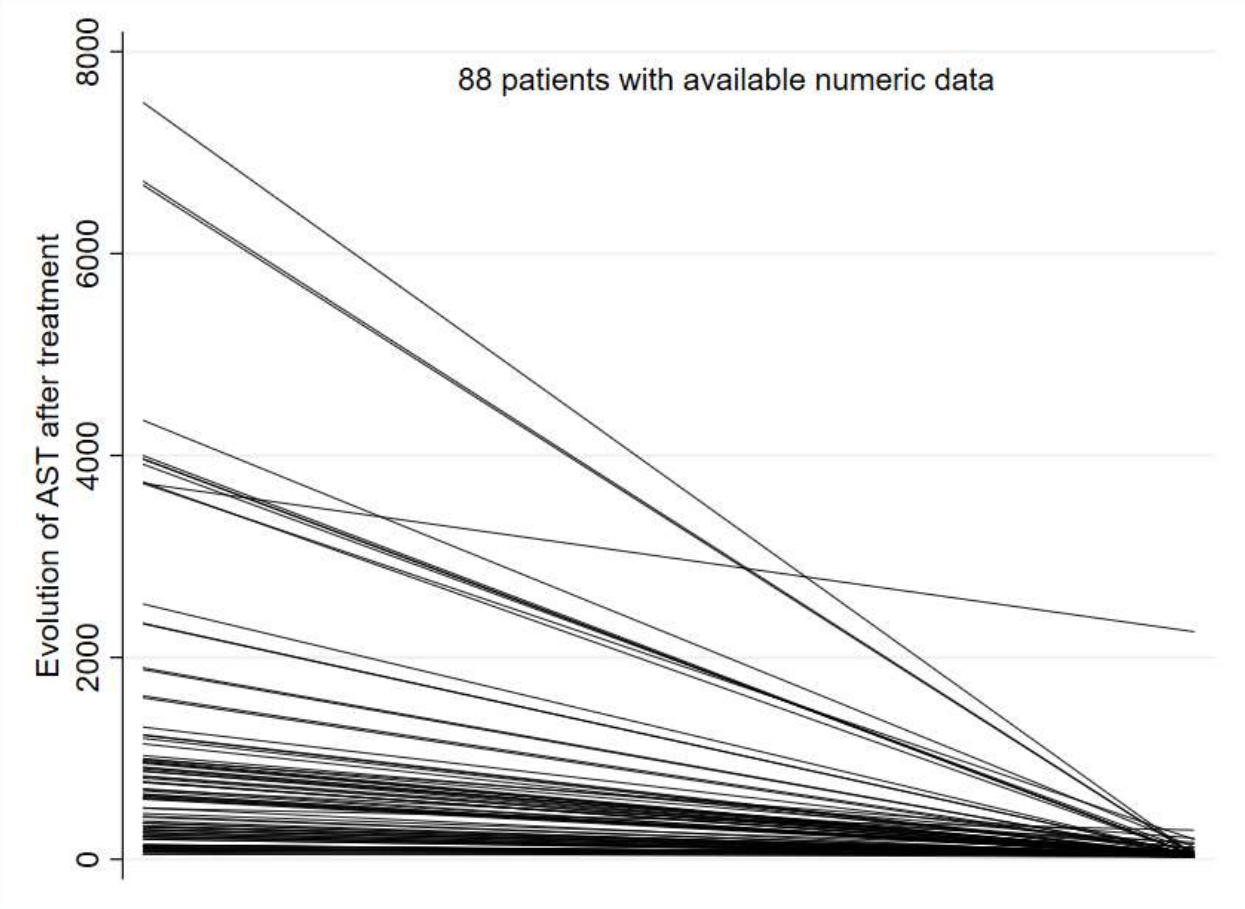
Diastase staining

Diastase digestion removing glycogen resulting in “ghost cells



Sweetser S et al. Hepatology. 2010;51(2):711–712.

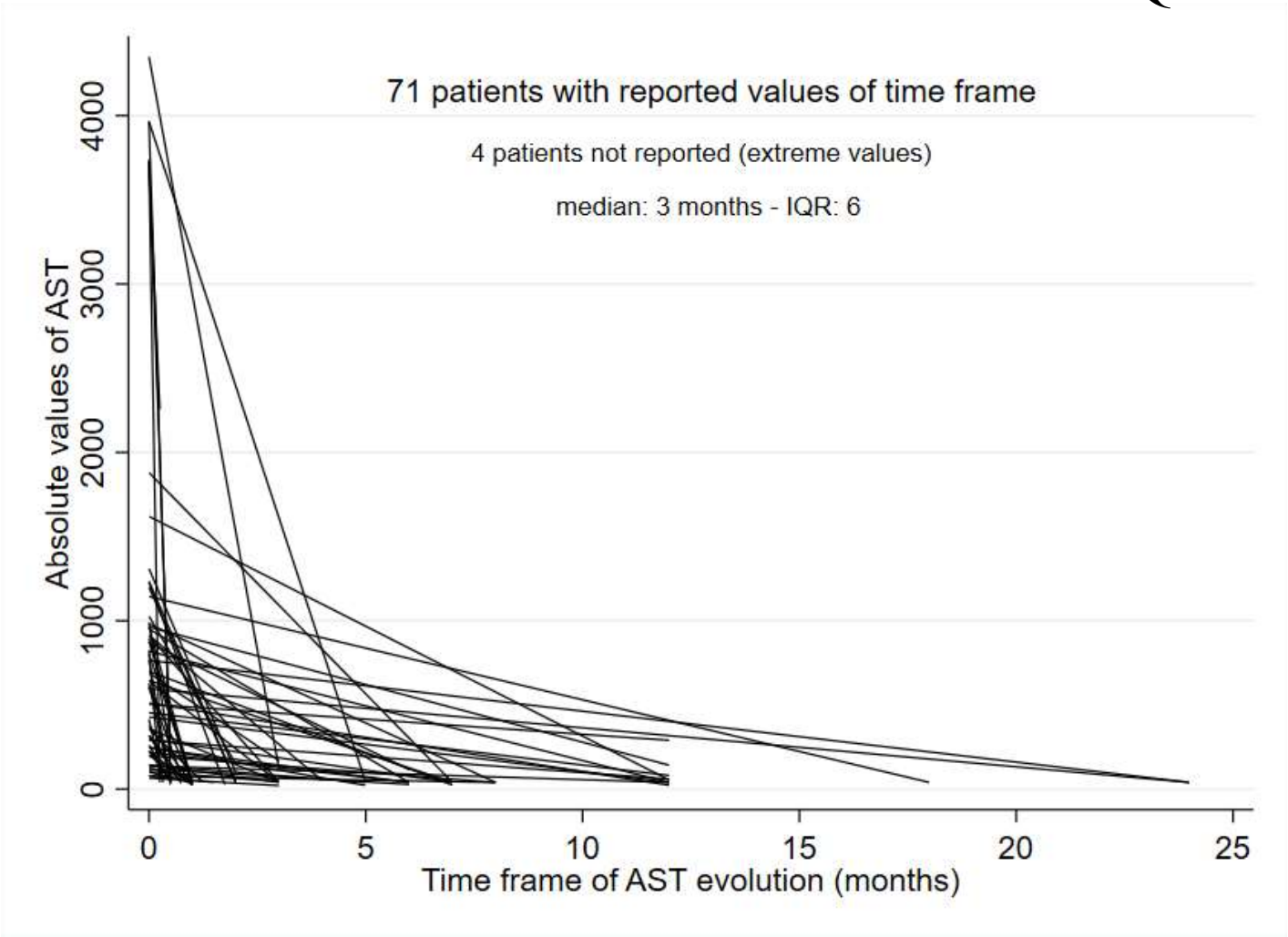
Evolution of AST after glycemic control



Haffar S et al. Liver International 2021;41:1545–1555.

Evolution of AST after glycemic control with time frame

Median interval for normalization 3 months – IQR 6



Haffar S et al. Liver International 2021;41:1545–1555.

AST normalization after improved glycemic control

- Multiple linear regression based on 88 patients with available values
- According to 6 variables:
  age, sex, children vs adult, presence or absence of diabetic ketoacidosis history, glycosylated hemoglobin at presentation, and magnitude of AST elevation (borderline, mild, moderate, severe)
- No statistically significant difference

Haffar S et al. Liver International 2021;41:1545–1555.

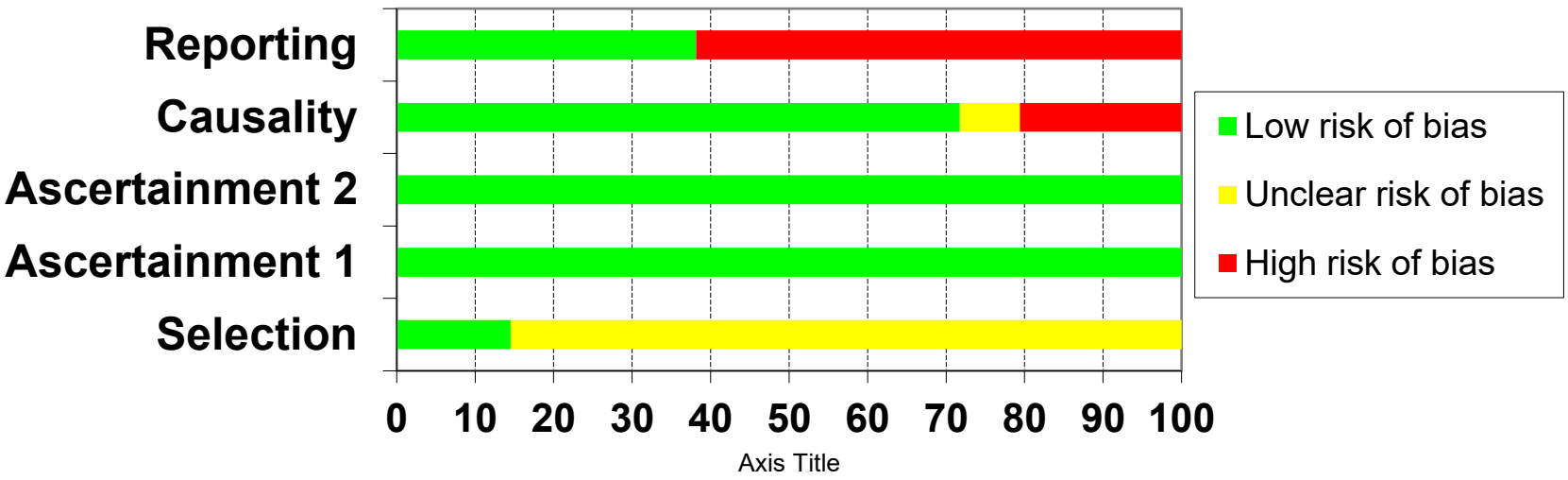
AST normalization after improved glycemic control

Multiple linear regression based on 88 pts with available values

AST normalization	Coefficient	Standard error	95% CI		p value
Age	.0076767	.0080283	–.0083936	.0237471	0.343
Children vs adult	–.1284077	.1517652	–.4321987	.1753834	0.401
Gender	.0726257	.123093	–.1737699	.3190249	0.557
Diabetic ketoacidosis	.10777	.1201198	–.132676	.3482159	0.373
HbA1c	–.358295	0.247334	–.0853388	.0136797	0.153
AST magnitude:					
- Mild	–.2043419	.3061476	–.8171629	.4084792	0.507
- Moderate	–.2853204	02851445	–.8560992	.2854584	0.321
- Severe	–.3805134	.2719128	–.9248061	.1637792	0.167
Constant	1.235802	.4835792	.2678135	2.203791	0.013

Haffar S et al. Liver International 2021;41:1545–1555.

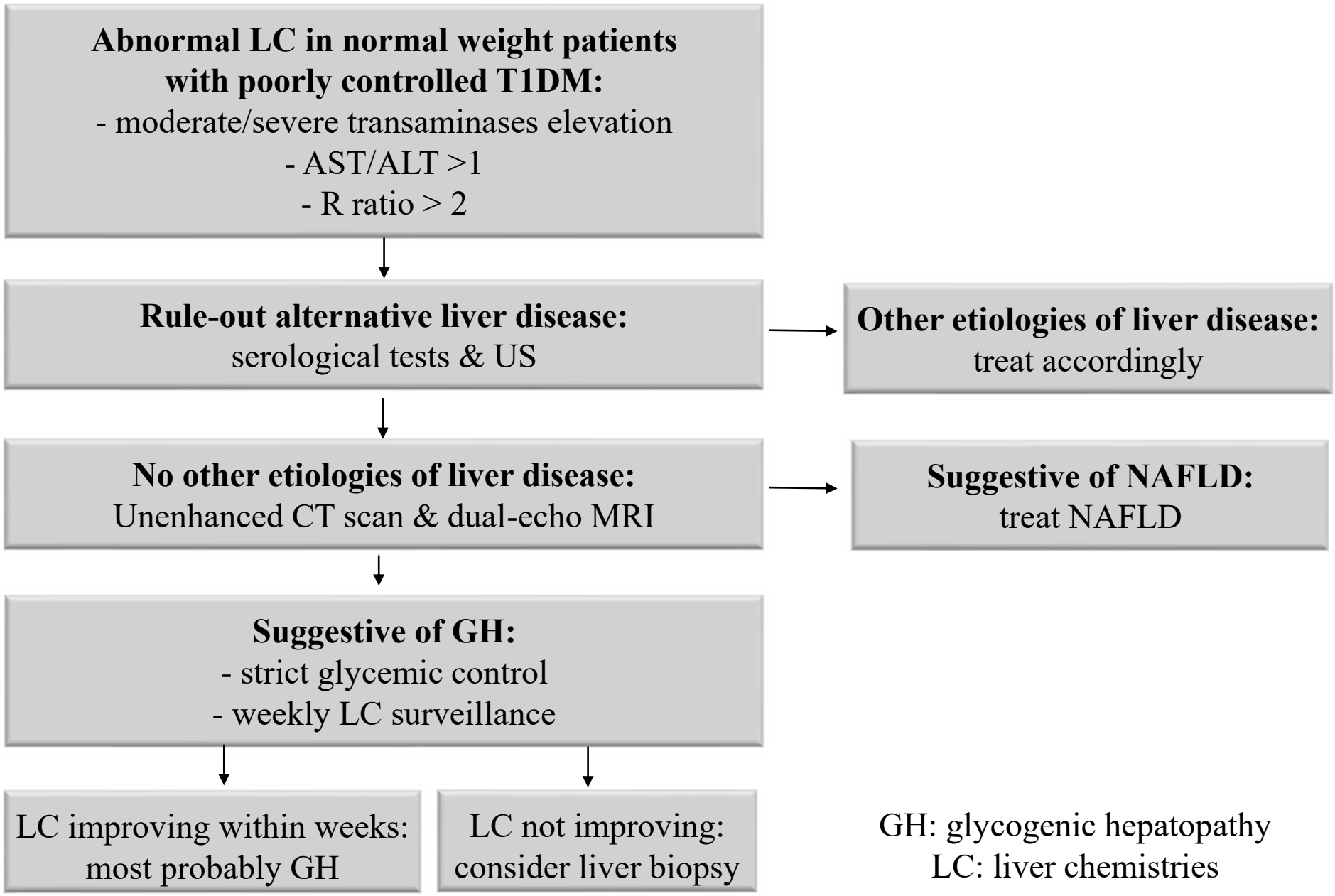
Assessment of methodological quality



Agreement between the two reviewers for the assessment of methodological quality: **93%**

Haffar S et al. Liver International 2021;41:1545–1555.

Diagnostic approach of GH in patients with T1DM



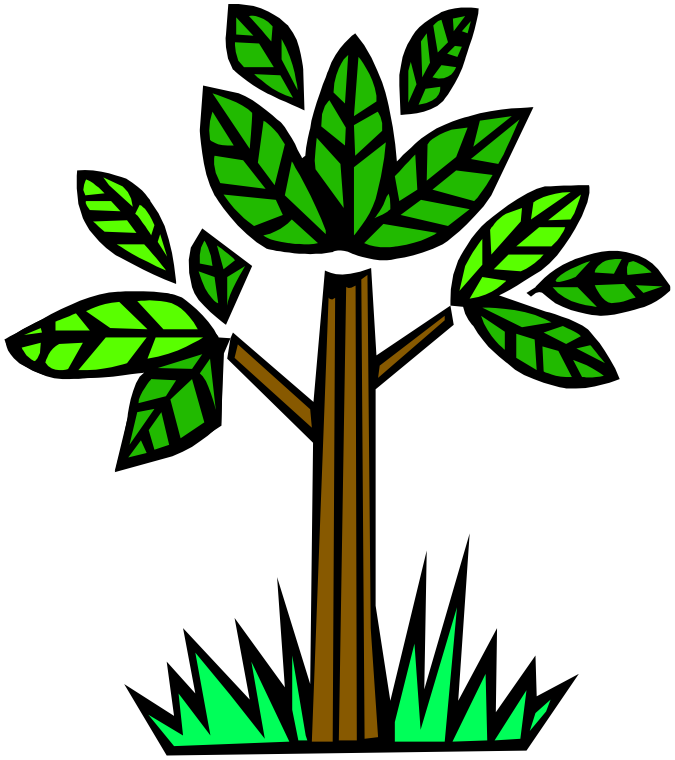
GH: glycogenic hepatopathy
LC: liver chemistries

Conclusion

- Moderate/severe elevation of transaminases, AST/ALT >1 and hepatocellular to mixed pattern of hepatic injury raise suspicion of GH in the appropriate clinical context
- GH should not be misdiagnosed as NAFLD: transaminase exceeds threshold observed in NAFLD in 60% of T1DM patients with GH
- Massive elevation of transaminases (>10 000 U/l) excludes GH
- Normal liver chemistries make GH highly unlikely
- Transaminases improve drastically in most patients after glycemic control within a median of 3 months

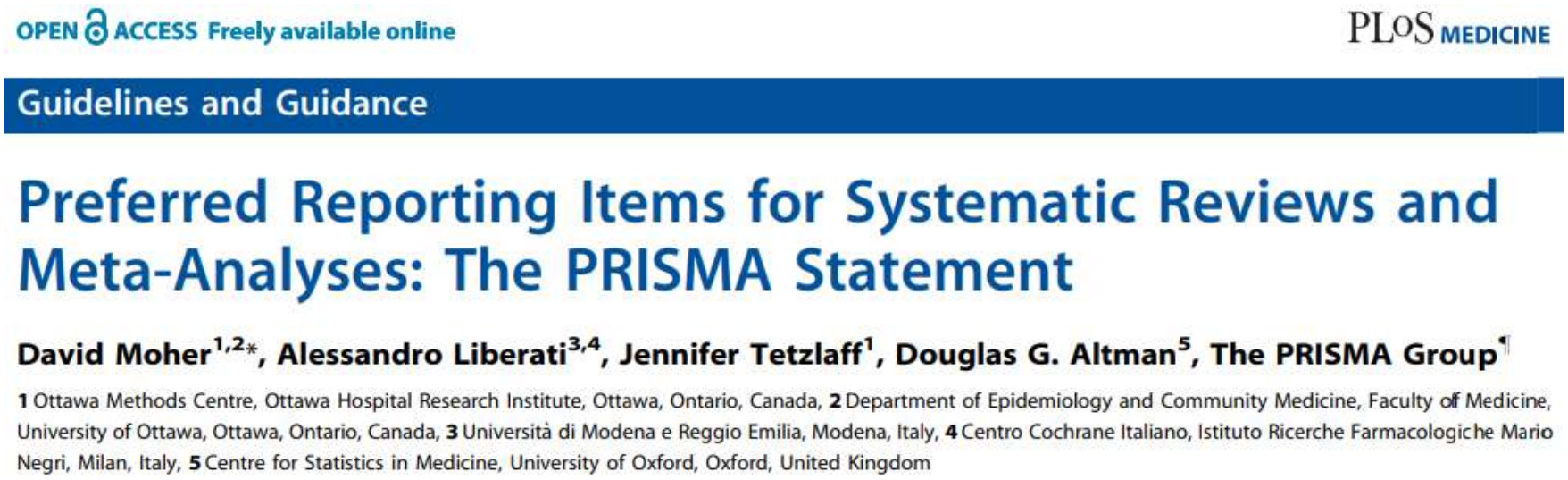
Haffar S et al. Liver International 2021;41:1545–1555.

Thank You



The PRISMA statement

Systematic review reported in line with the guidelines of the preferred reporting items for systematic reviews and meta-analyses (**PRISMA**) with an *a priori* study protocol



OPEN ACCESS Freely available online

PLoS MEDICINE

Guidelines and Guidance

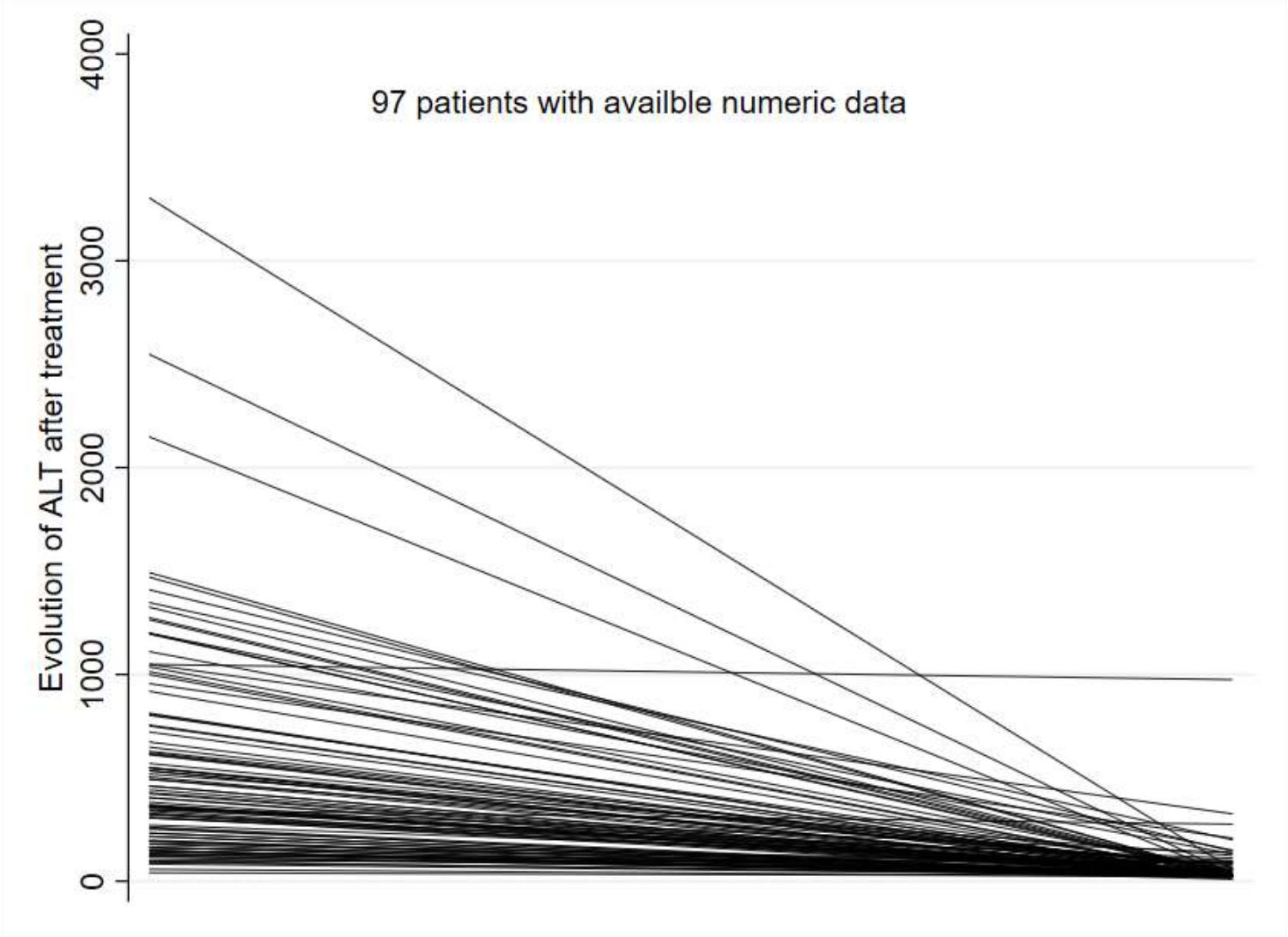
Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

David Moher[1,2]*, Alessandro Liberati[3,4], Jennifer Tetzlaff[1], Douglas G. Altman[5], The PRISMA Group[¶]

1 Ottawa Methods Centre, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada, **2** Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada, **3** Università di Modena e Reggio Emilia, Modena, Italy, **4** Centro Cochrane Italiano, Istituto Ricerche Farmacologiche Mario Negri, Milan, Italy, **5** Centre for Statistics in Medicine, University of Oxford, Oxford, United Kingdom

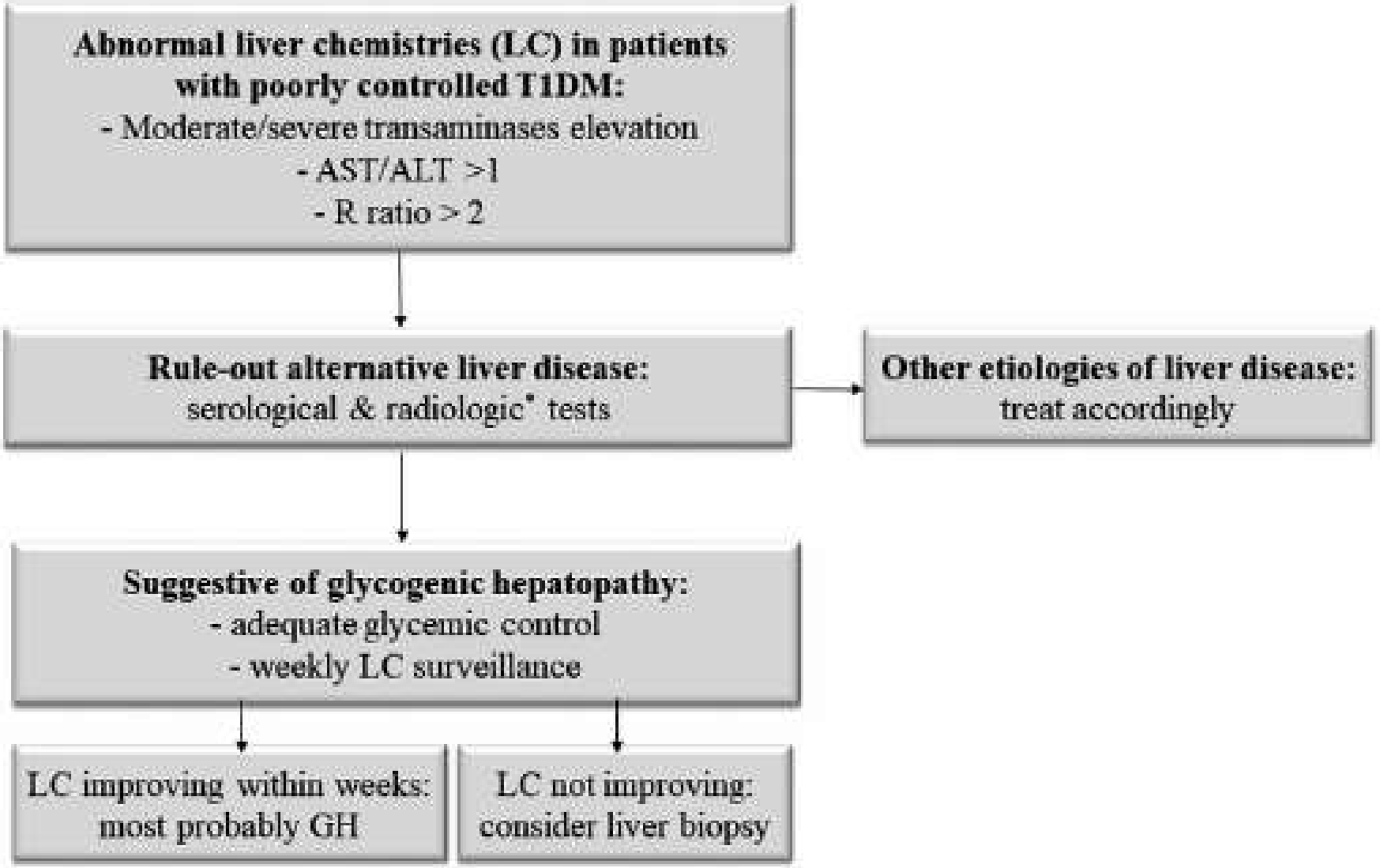
Moher D et al. PLoS Medicine. 2009;6(7):e1000097.

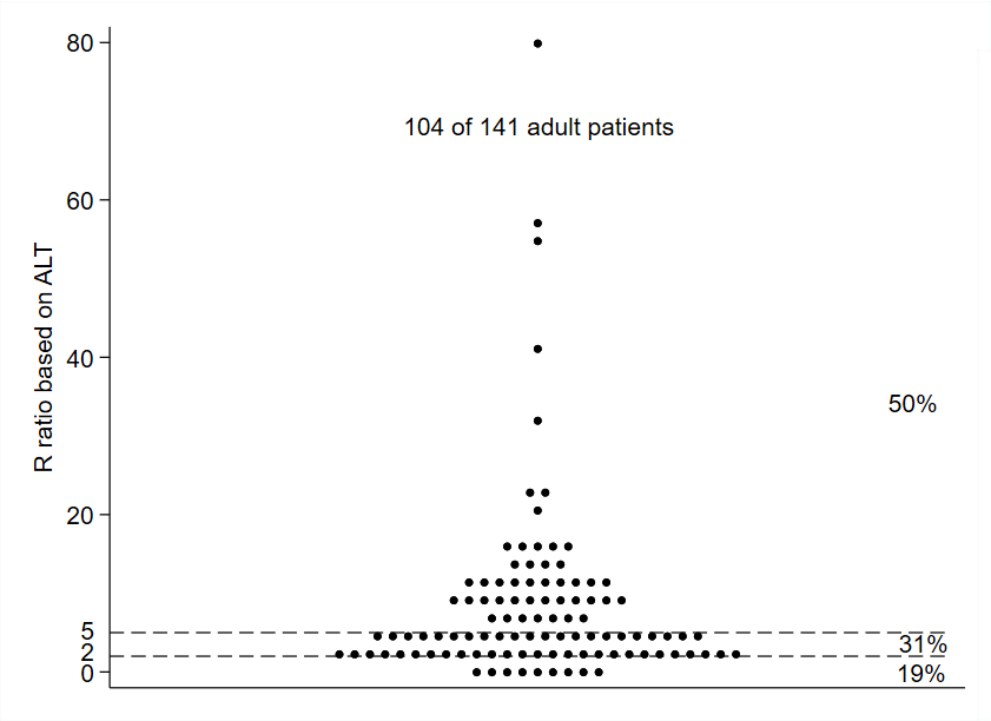
Evolution of ALT after glycemic control

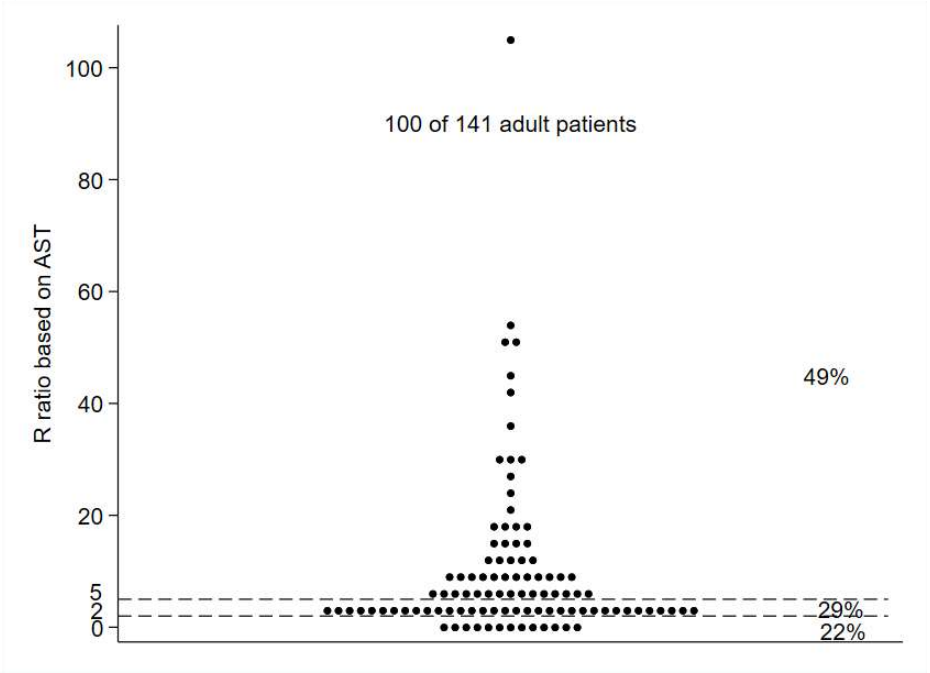


Haffar S et al. Liver International 2021;41:1545–1555.

Diagnostic approach of GH in patients with T1DM




80
60
40
20
5
2
0
R ratio based on ALT
104 of 141 adult patients
50%
31%
19%


100
80
60
40
20
5
2
0
R ratio based on AST
100 of 141 adult patients
49%
29%
22%