Derin Sarılık ve İNR Artışı Olan Hasta; Ayırıcı Tanıyı Nasıl Yapalım?

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ANKARA ŞEHİR HASTANESİ

OLGU

41 yaş erkek hasta
Sarılık ve kaşıntı

Öykü: 20 gün önce ciltte sararma ve kaşıntı şikayeti ile dış merkeze başvuru
Eşi COVİD +, hastanın benzer semptomları olmuş. test vermemiş. Parasetamol ve NSAİİ (ibuprofen) kullanımı var

1 yıl önce KCFT yüksekliği ve **kaşıntı** nedeniyle dış merkez başvuru
NSAİİ kullanımı (+) (ibuprofen)

03/05/2021
ALT/AST:53/24, ALP/GGT:241/23, T/D BİL:0,4/0,1
ELİSA: Negatif
ANA, ASMA, AMA, LKM: Negatif

Özgeçmiş: Özellik yok
Soygeçmiş: Özellik yok

Fizik muayene:
Skleralar:ikterik
Cilt :Sarılık
Sistem muayeneleri normal

Kullandığı ilaçlar: Yok
Alkol: Ayda 1 kez rakı içme öyküsü var

AKŞ: 106 mg/dl
Üre: 19 mg/dl
Kre: 0.65 mg/dl
AST:51 IU/L
ALT:58 IU/L
ALP:446 IU/L
GGT: 21 IU/L
T.pro/alb: 7.7/4.3 mg/dl
T.bil/D.bil: 16.3/12.7 mg/dl
Ürik asit: 3.4
Na: 136 mEq/L
K: 4.6 mEq/L
Hb:15 mg/dl
Lök: 7240x10^6/L
Plt: 317x$10^{9/}$L
INR: 2.3
PTZ: 25 sn
AFP: 1.3 µg/L
Ferritin: 339
TS: %21

HbsAg : Negatif
Anti Hbc Total: Negatif
Anti-HCV: Negatif
Anti-HAV Ig M: Negatif
Anti-HIV: Negatif
TORCH PANELİ:Negatif

ANA: Negatif
AMA: Negatif
Anti-LKM: Negatif
ASMA: Negatif
ANCA paneli: Negatif
Ig G: 14.1 g/L
Ig A: 1.77 g/L
Ig M: 1.18 g/L

Seruloplazmin: 0.59 g/L
Bakır (24 saatlik idrar):82.28
Doku Tg Ig A: < 2
Anti-Ds DNA: Negatif
KF halkası: İzlenmedi
Paterji Testi: Negatif
Covid Ac: Negatif
A1 Antitripsin: Normal

Abdomen USG:

- Karaciğer kraniokaudal boyutu 173 mm ile normalden büyük olup parankim eko şiddeti grade 1 steatoza sekonder artmıştır. Karaciğer 7. subsegmentte 14 mm ebatlı, 6. subsegmentte 11 mm ebatlı hiperekoik hemanjiom ile uyumlu görünüm izlenmiştir.

- İntrahepatik safra yolu dilatasyonu saptanmamıştır.

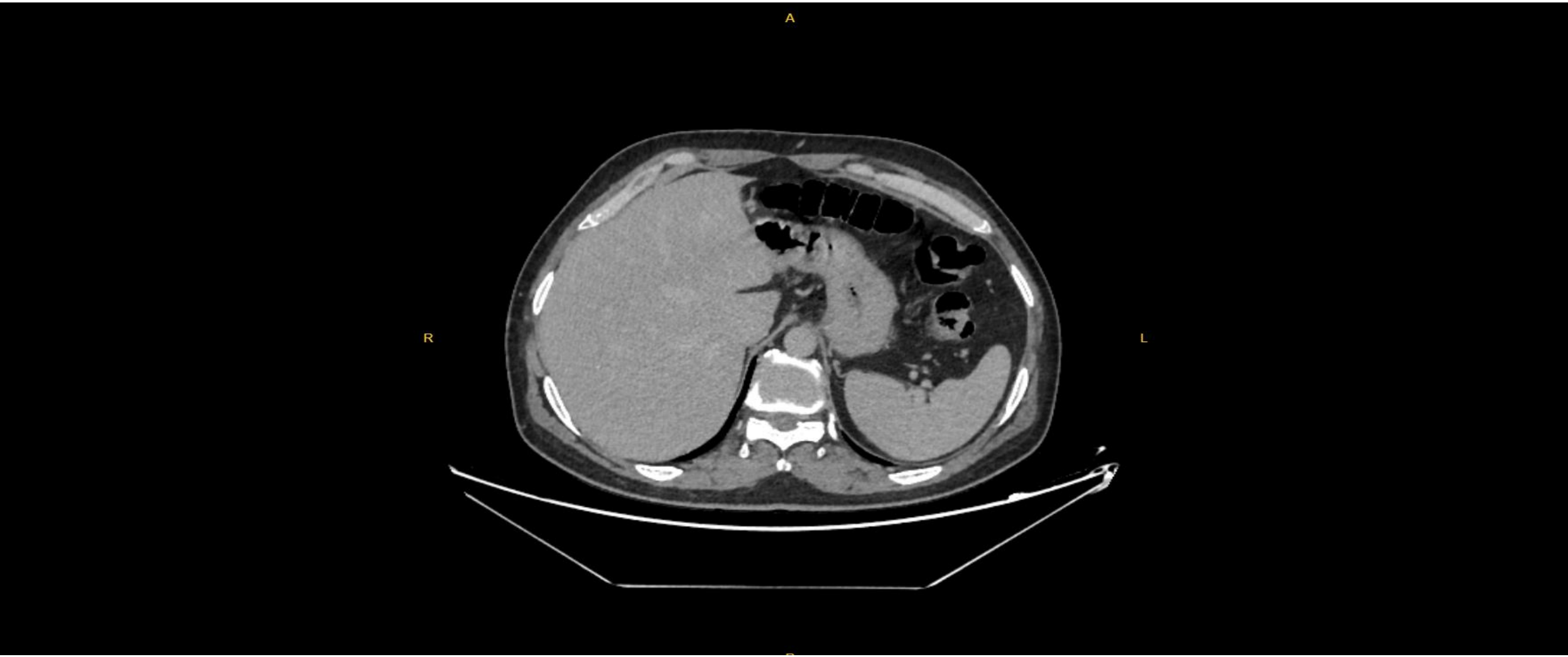
- Doppler USG; normal

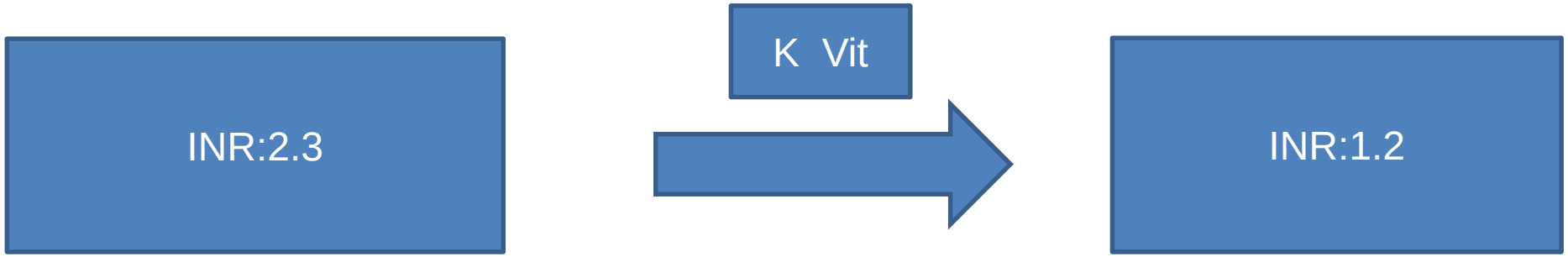
Dinamik Abdomen BT:

- Karaciğer normal konum ve boyuttadır. Karaciğer konturları düzgün, parankim dansitesi diffüz azalmış görünümde izlenmektedir. Karaciğer sağ lob 7-6. segmentte büyüğü 6mm boyutunda olan 2 adet hemanjiom ile uyumlu lezyon; intra ve ekstrahepatik safra yolları normal

- Dalak normal konum ve boyuttadır. Parankimi homojendir. Splenoportal aks açıktır.

- Pankreas normal konum ve boyuttadır.Parankimi homojendir.


A
R
L


INR:2.3
K Vit
INR:1.2

SARILIK AYIRICI TANISI

Öykü, fizik inceleme, CBC, biyokimya

İzole Hiperbilirübinemi
Sarılık dışında hepatobiliyer semptom yok
KCFT normal

İNDİREKT BİLİRÜBİN

Gilbert sendromu
Hemoliz
İlaç

Crigler-Najar tip 2

DİREKT BİLİRÜBİN

Dubin-Johnson
Rotor sendromu

KCFT bozukluğu ve Hiperbilirübinemi
Sarılık dışında semptomlar var
Altta yatan hastalığın ipuçları

USG
(yetersiz olursa BT)

Safra yolları dilate

Ekstrahepatik kolestaz

MRCP
EUS
ERCP
PTK

T-T-S
Taş-tümör-striktür

Safra yolları normal

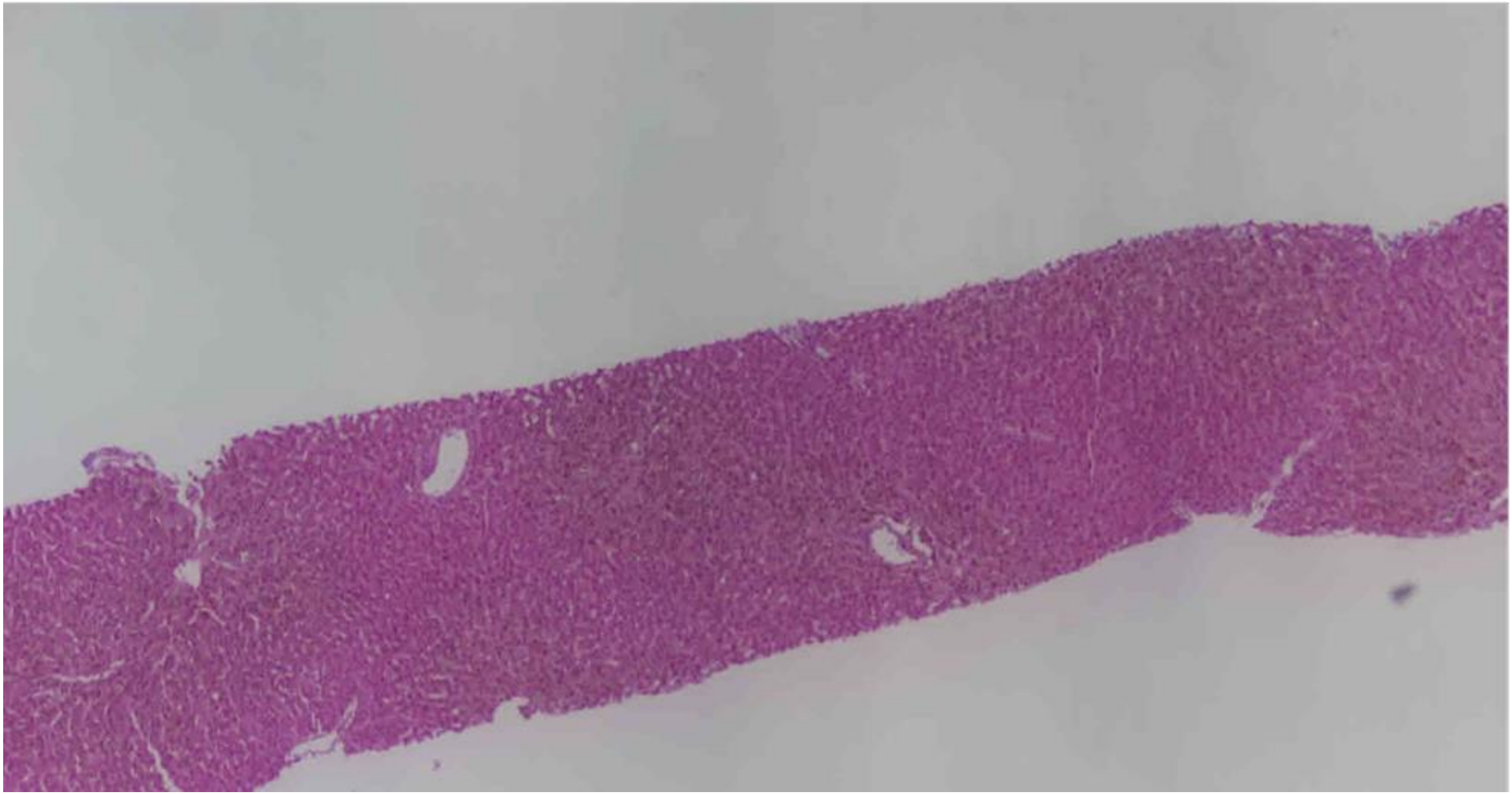
Hepatoselüler sarılık
İntrahepatik kolestaz

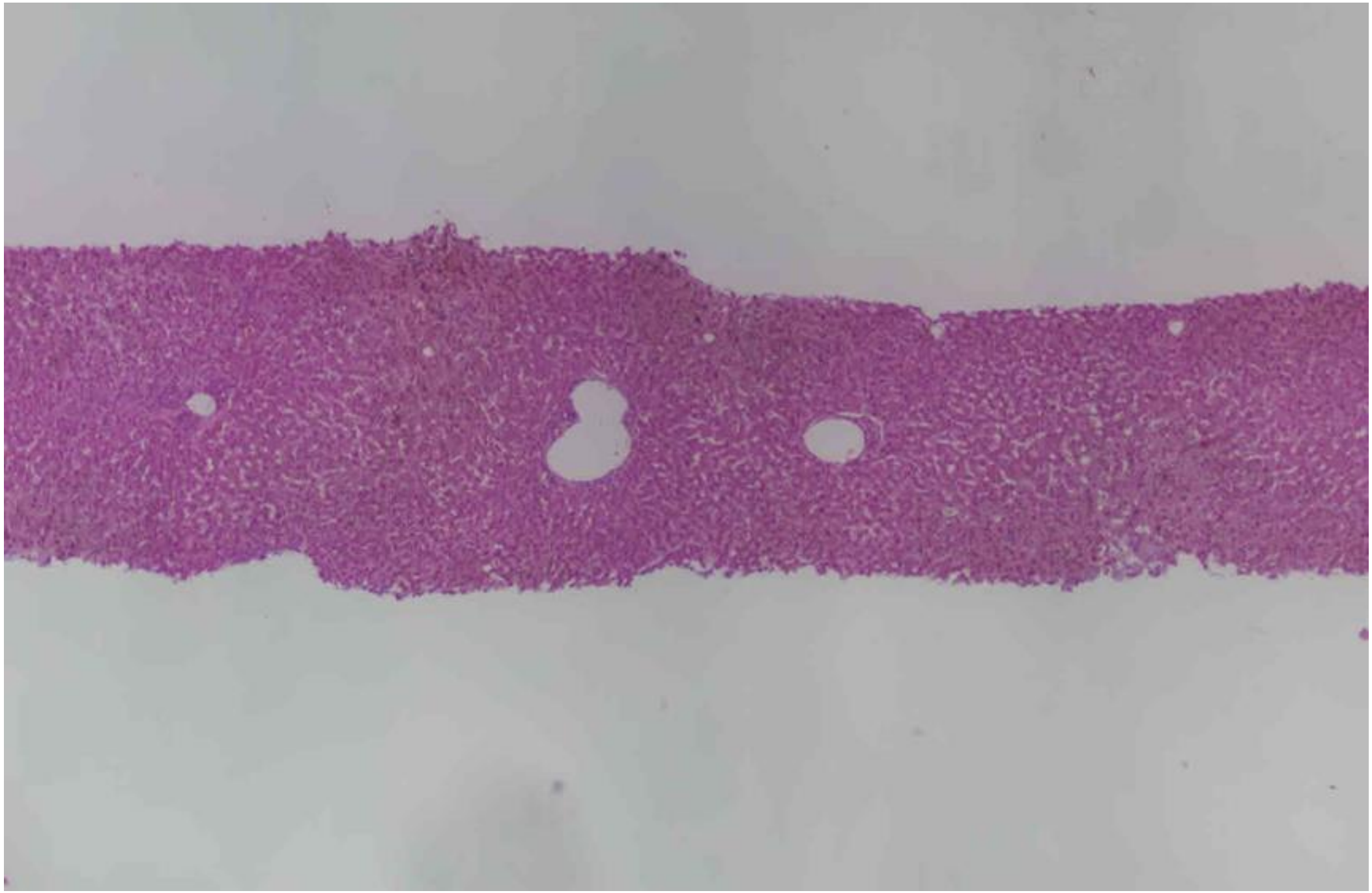
Seroloji
(viral, otoimmün)
Alkol, ilaç öyküsü
Metabolik hastalık testleri
Karaciğer biyopsisi
Genetik testler

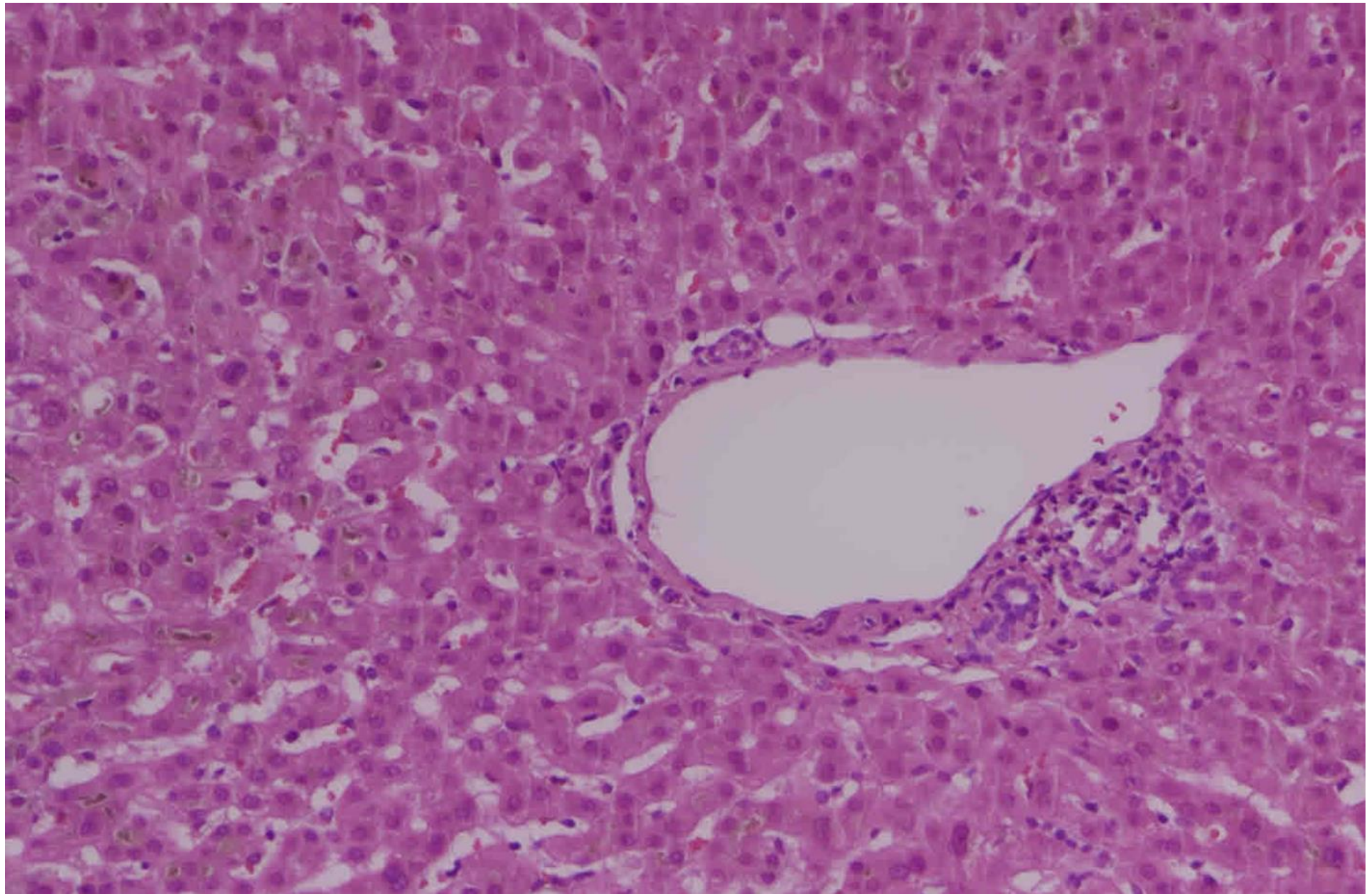
İntrahepatik Kolestaz

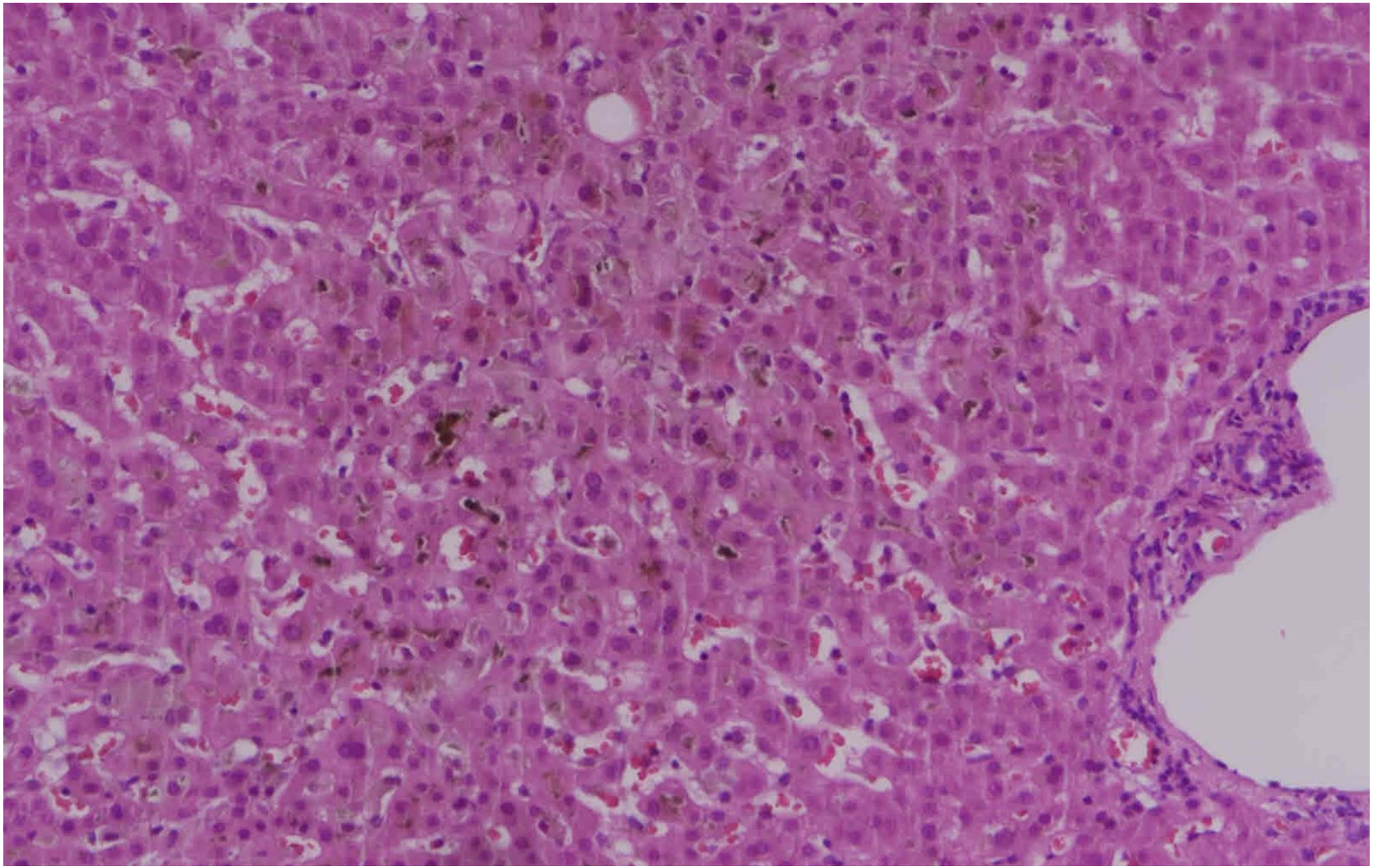
- Viral hepatitler
- Alkolik hepatit
- Non-alkolik steatohepatit
- Kronik hepatitler
- Primer biliyer kolanjit
- İlaçlar ve toksinler
- Sepsis ve hipoperfüzyon durumları
- Kalıtsal kolestazlar (BRİC, PFIC)

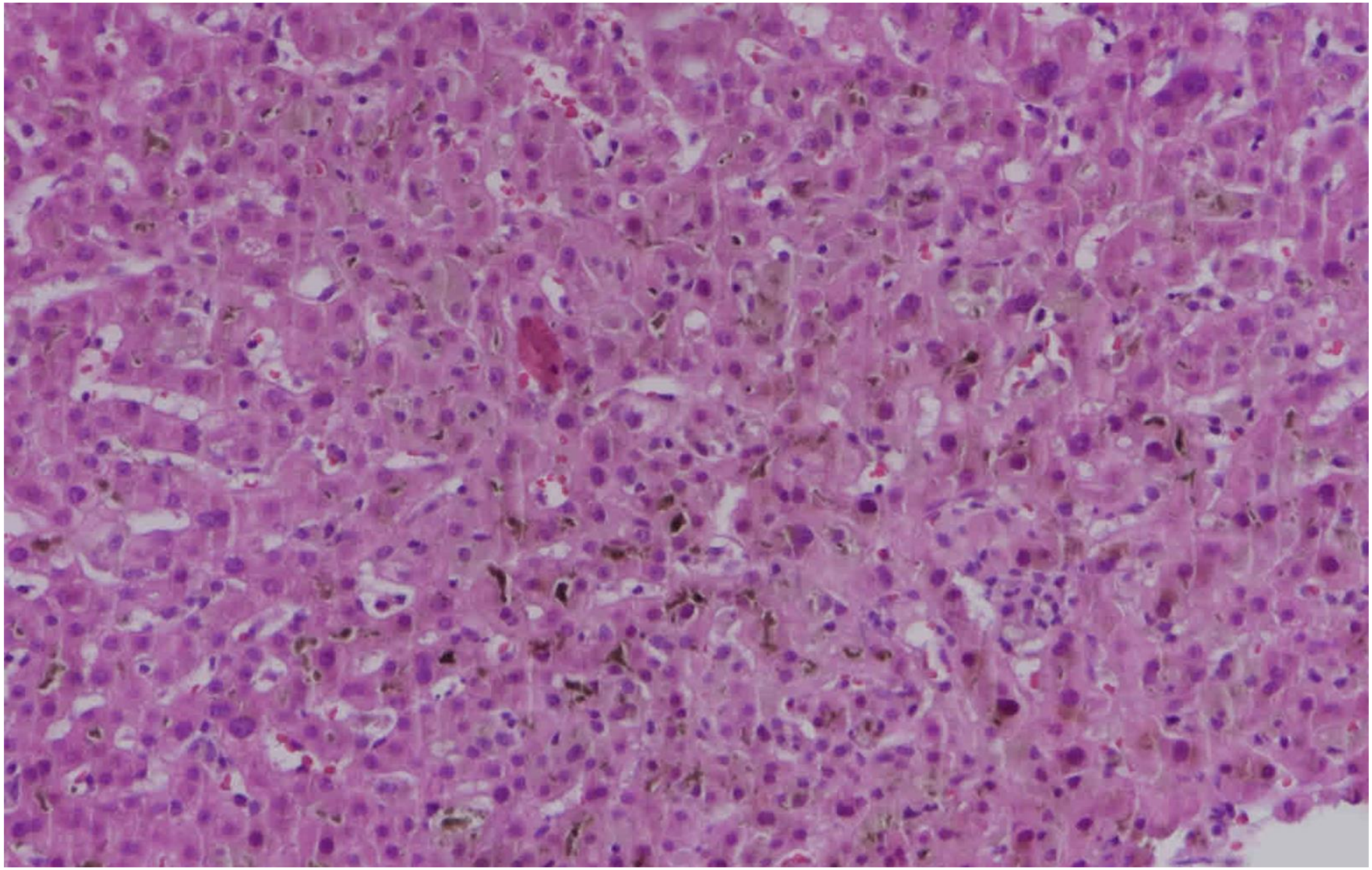
- İnfiltratif hastalıklar (sarkoidoz,Tbc, lenfoma, amiloidoz)
- TPN
- Postoperatif kolestaz
- Organ nakil
- Orak hücre anemisi hepatik kriz
- Gebelik
- Son dönem karaciğer hastalığı

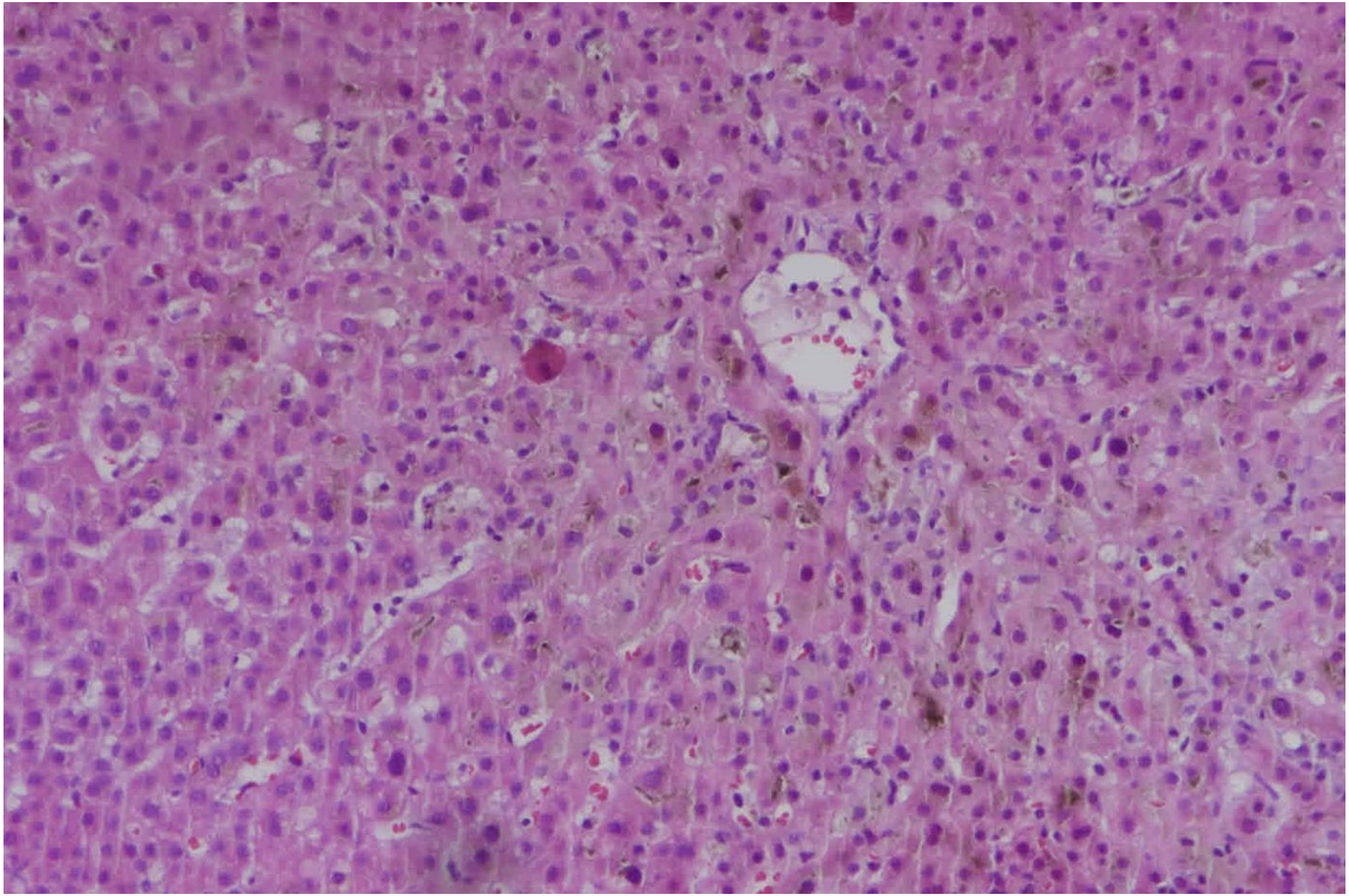


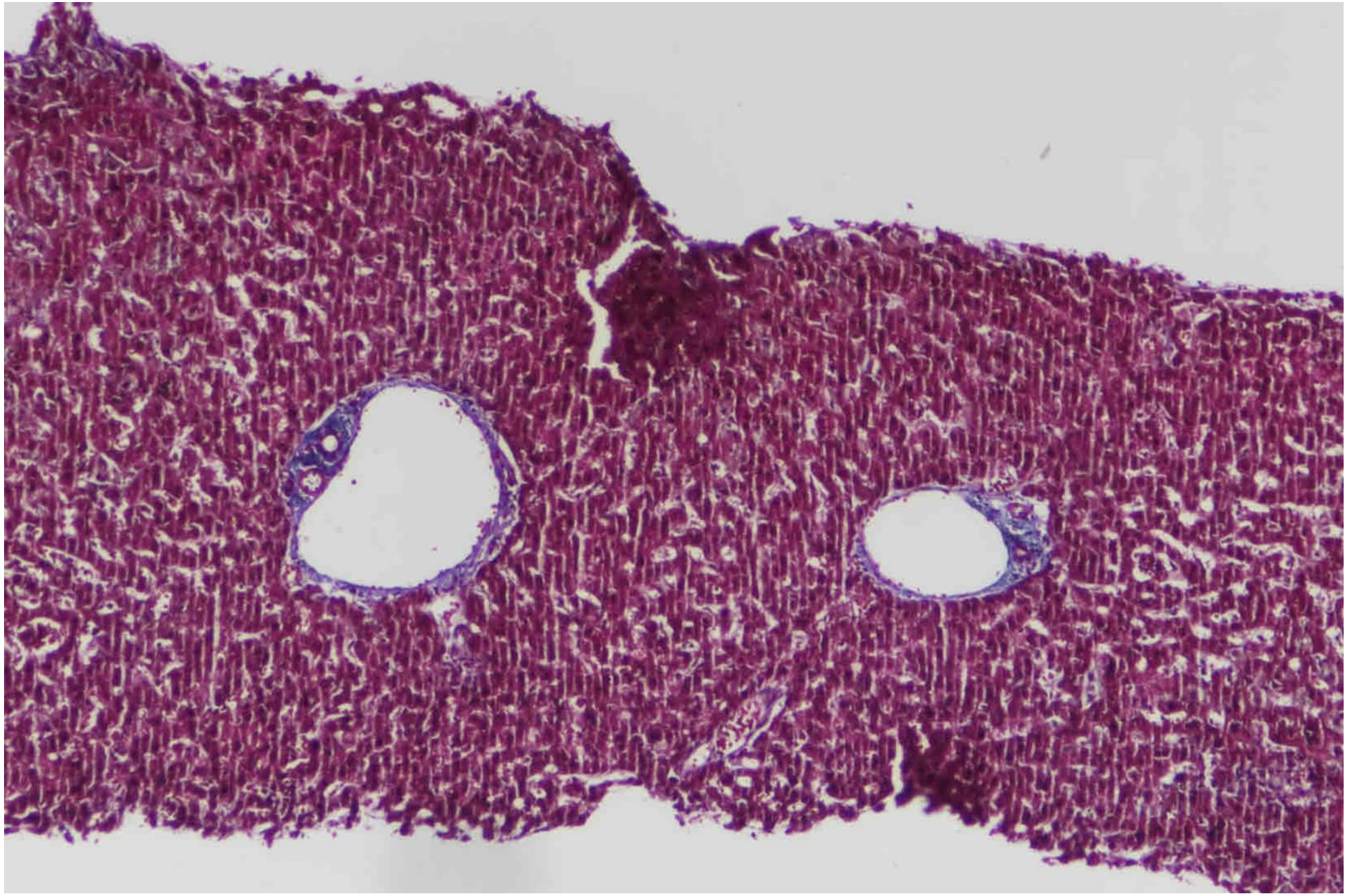


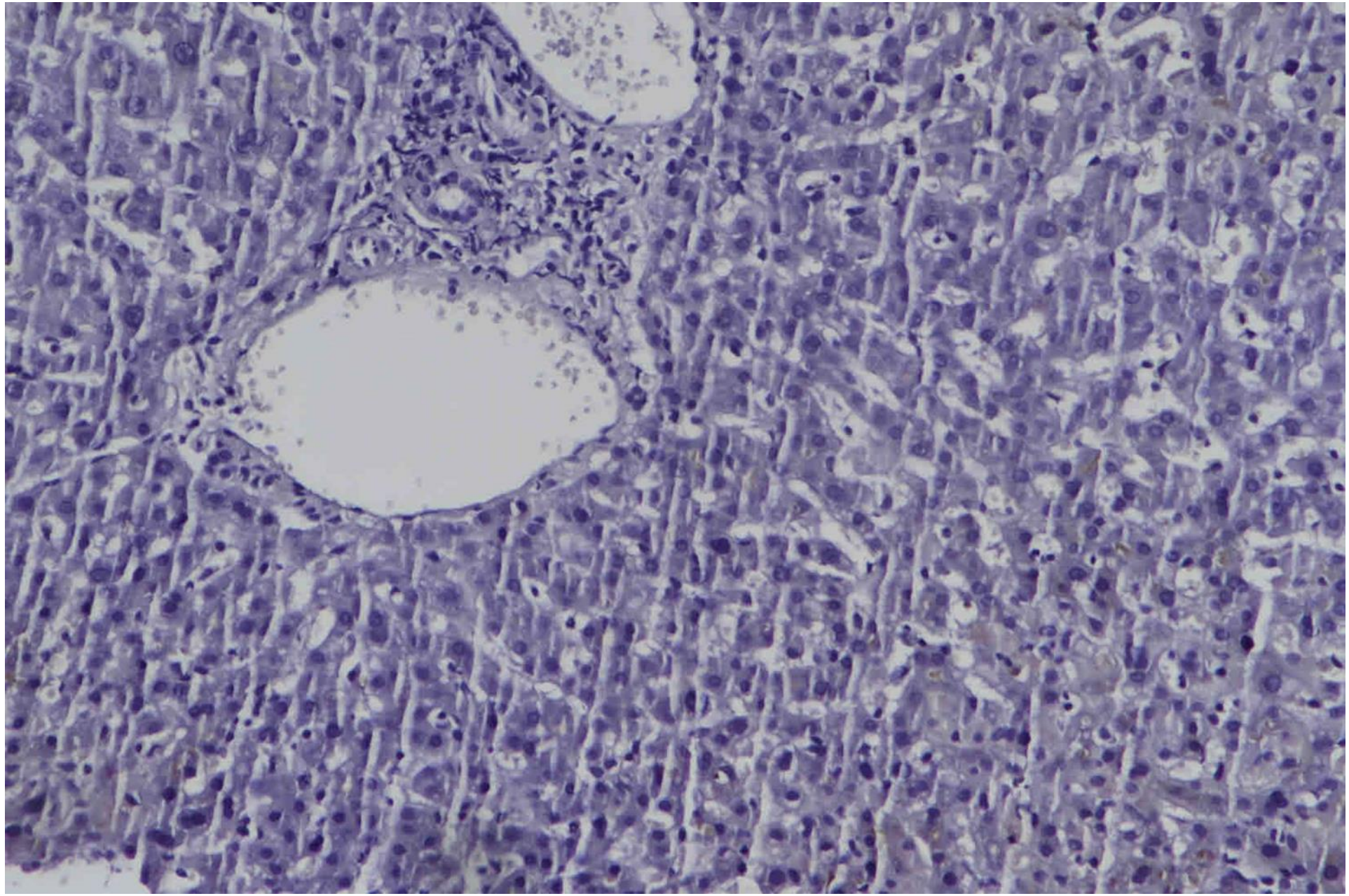


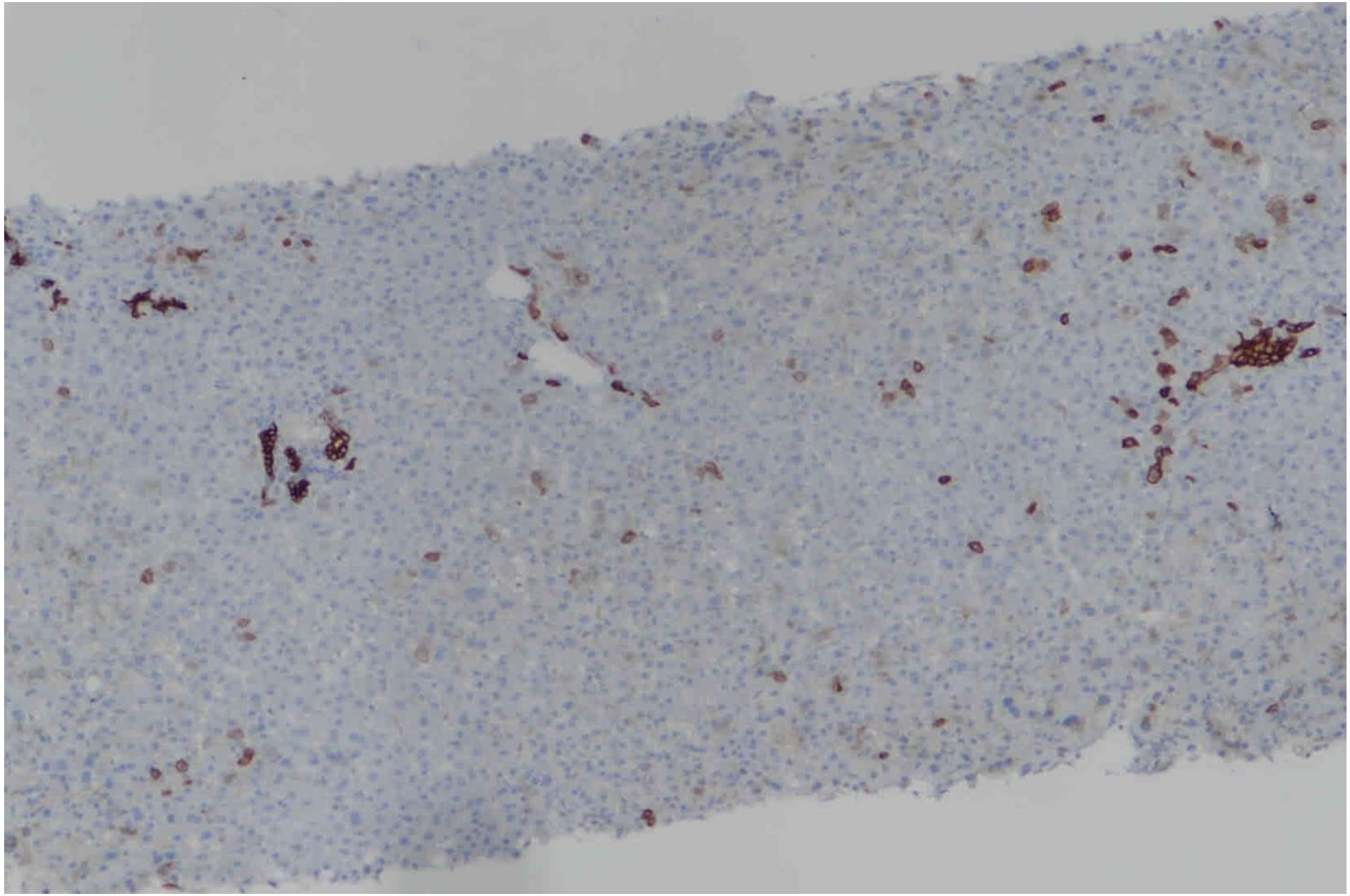












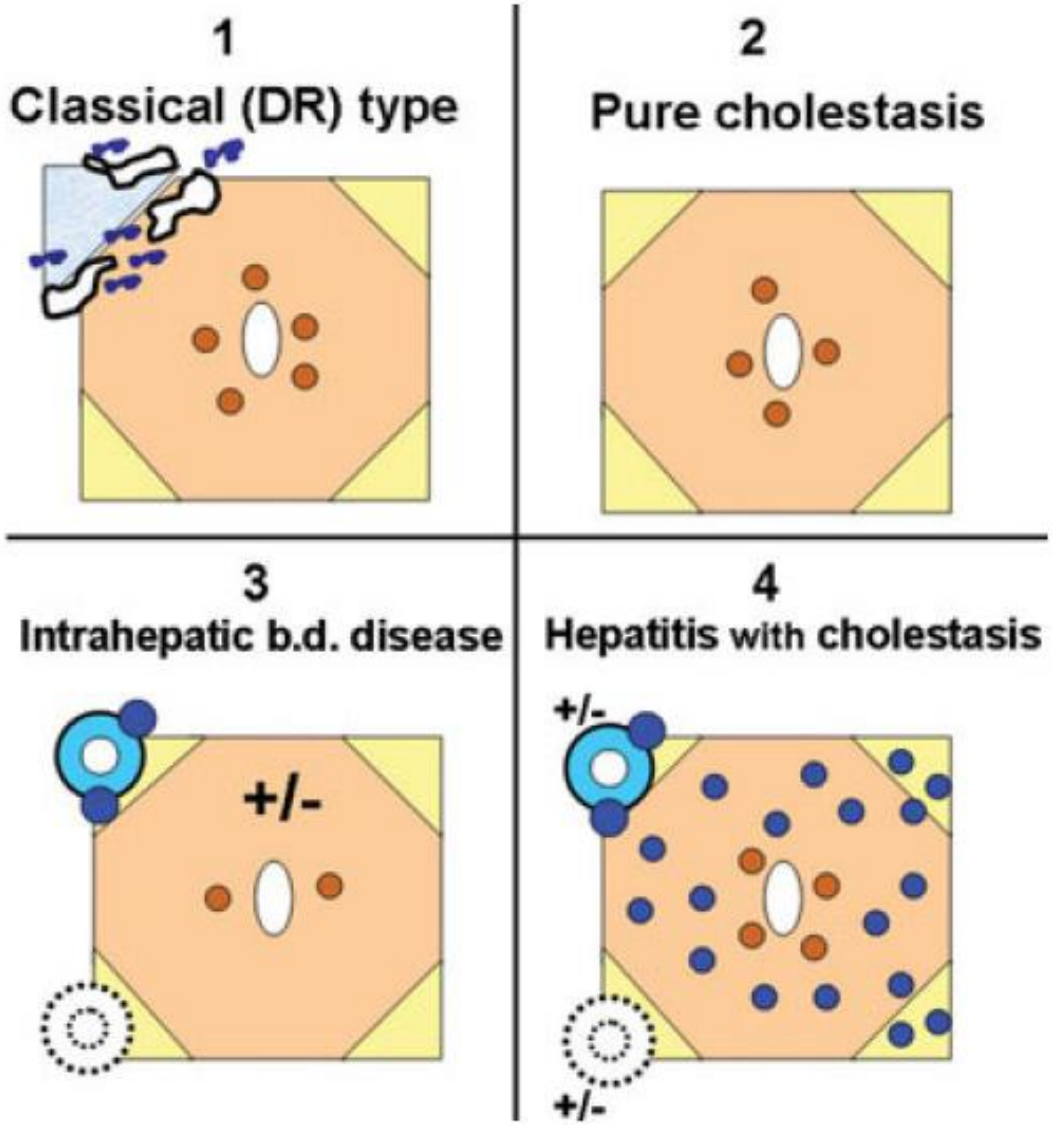
MAKROSKOPİ	12 mm 6 mm 2 mm uzunluğunda 3 adet doku parçası tamamı 3P1K Tek gözde 04 04 22
MİKROSKOPİ	İncelenen kesitlerde temel striktür korunmaktadır ve 15 adet portal alan mevcuttur. Portal alanlarda hafif eozinofil ve tek tük mononukleer iltihabi hücreler bulunmaktadır. Portoparankimal sınır sağlamdır, interface hepatitisi yoktur. İntraasiner nekroinflamatuar odak/apoptozis görülmemiştir. Parankimde zon 3te daha yoğun olmak üzere hepatoselüler ve kanaliküler kolestaz izlenmiştir.
UYGULANAN ÖZEL YÖNTEMLER	910.360 - Karaciğer, Biyopsi İğne / Wedge (Kama) / 911.160-5 - Histokimyasal Boyamalar - Massosn´s Trichome Masson trikrom boyasında fibrozis görülmemiştir.
TANI	**KOLESTAZ (HEPATOSELÜLER VE KANALİKÜLER); karaciğer, Trucut biyopsi**
ICD-O KODU	0000/0 - Neoplazma rastlanmamıştır.
YORUM / NOT	Morfolojik bulgular herhangi bir hastalık için spesifik olmayıp hastanın toksik nedenler başta olmak üzere kolestaz yapan nedenler açısından araştırılması ve klinikopatolojik korelasyon önerilir.

ACUTE CHOLESTASIS

portal edema
ductular reaction
neutrophils

bile duct damage

ductopenia



(PURE) saf kolestaz nedenleri

Drugs (steroids, oral contraceptives)

Sepsis

Early stages of large bile duct obstruction

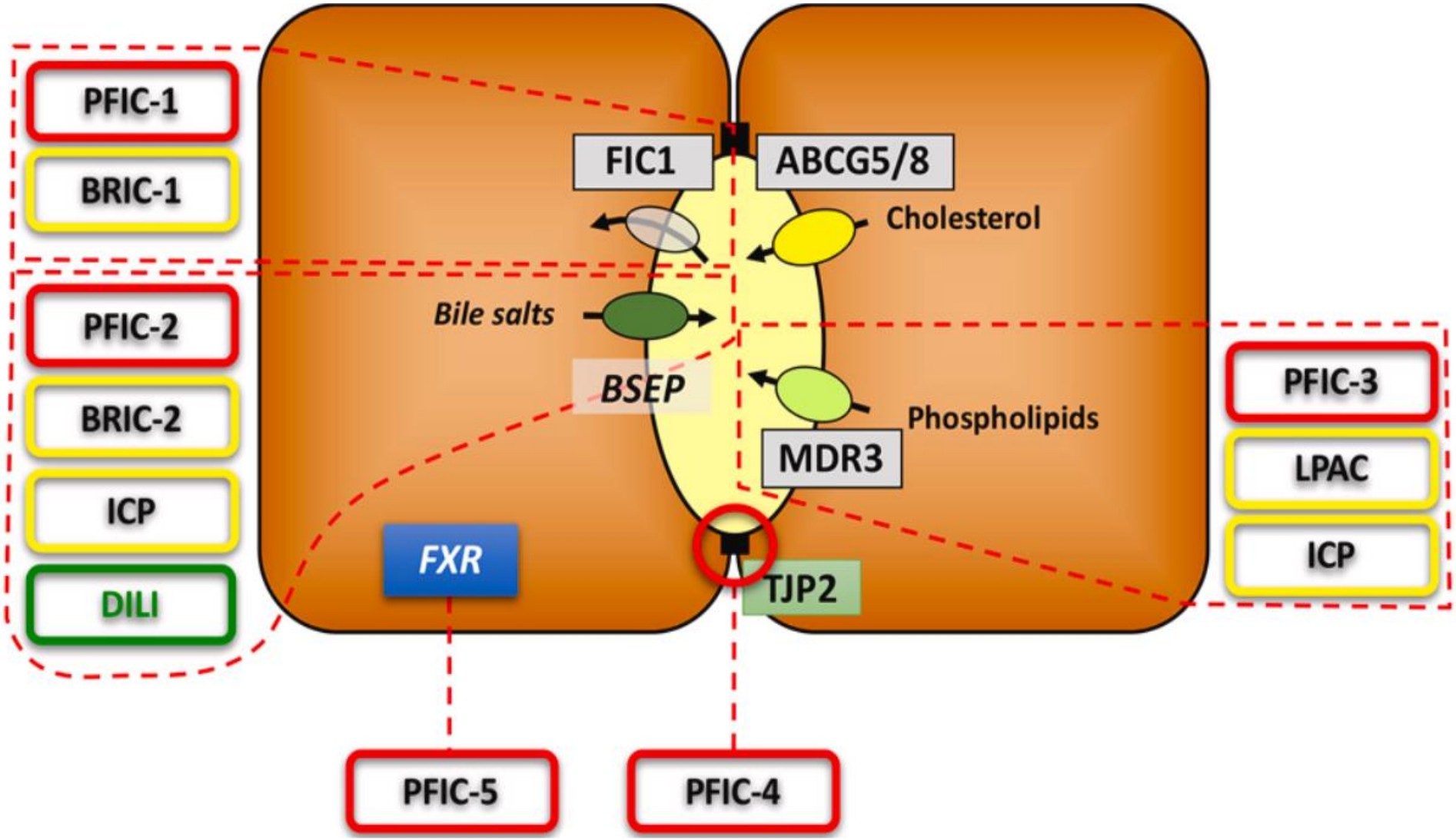
Genetic disorders

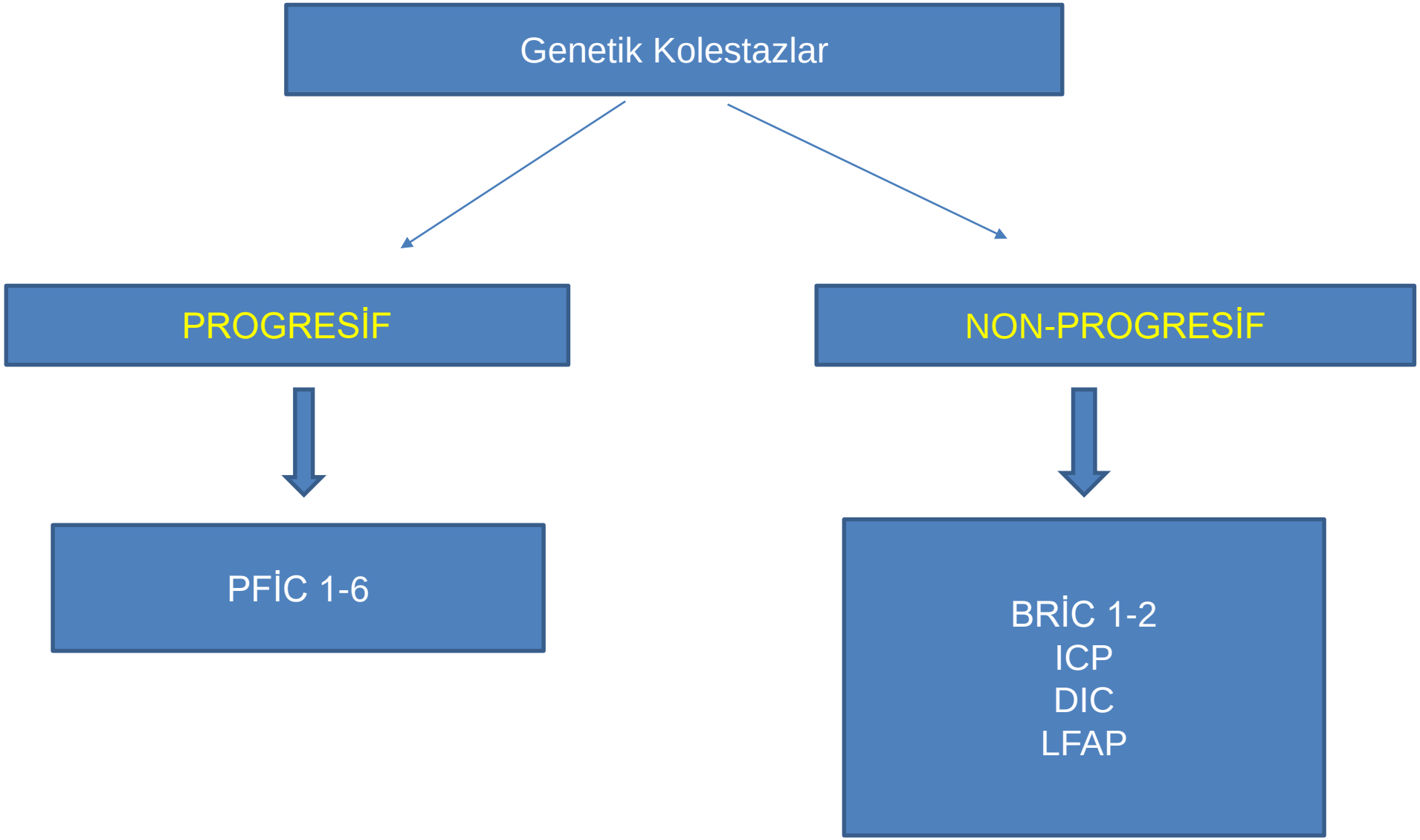
Jaundice of pregnancy

Thyroid diseases (hypo or hyperthyroidism)

Paraneoplastic syndromes (lymphoma, carcinoma)

Genetik kolestatik hastalıklar




Genetik Kolestazlar
PROGRESİF
NON-PROGRESİF
PFİC 1-6
BRİC 1-2
ICP
DIC
LFAP

	Progressive familial intrahepatic cholestasis					
	PFIC 1	PFIC 2	PFIC 3	PFIC 4	PFIC 5	PFIC[b]
Locus/gene/protein	18q21-22/ATP8B1/FIC1	2q24/ABCB11/BSEP	7q21/ABCB4/MDR3	9q21.11/TJP2/ZO-2	12q23.1/NR1H4/FXR	18q21.1/MyosinVB/MYO5B
Clinics	Early onset; severe jaundice/itching; growth retardation; diarrhea, pancreatitis, deafness; leads to LT;	Early onset, severe jaundice/itching; leads to LT; potential post-LT recurrence	Childhood/young adulthood onset; can be drug-triggered; hepatomegaly, growth retardation, HCC risk;leads to LT	Early severe cholestasis onset; Progression to liver failure in childhood; No post-LT recurrence; HCC risk	Neonatal onset, rapid progression to ESLD, vitK-independent; coagulopathy	Onset < 2 years: ± MVID, jaundice/itching; hepatomegaly
Laboratory[a]						
BA	High	Very high	High	High	High	High
GGT	Low or normal	Low or normal	High	Normal or mild elevation	Normal	Normal
AST/ALT	Mild elevation	Moderate elevation	Mild elevation	Elevation	Moderate elevation	Mild or moderate elevation
AFP	Normal	High	Normal	High	High	Normal
Histology	Mild cholestasis, mild lobular fibrosis and inflammation with giant cells	Canalicular cholestasis, lobular/portal fibrosis and inflammation with giant cells	Loss of MDR3 expression, portal inflammation, portal fibrosis, cholestasis, ductular proliferation	Centrolobular cholestasis; mislocalization of claudin	Cholestasis, loss of BSEP expression	Cholestasis, Inflammation with giant cells, BSEP and MDR3 tissue expression, MYO5B and RAB11 A canalicular staining

PFIC: progressive familial intrahepatic cholestasis; BRIC: benign recurrent intrahepatic cholestasis; ICP: intrahepatic cholestasis of pregnancy; DILI: drug induced cholestasis; LPAC: low-phospholipid-associated cholelithiasis; BSEP: biliary salt export pump; MDR-3: class III multidrug resistance P-glycoprotein; TJP-2: tight junctions protein-2; zo-2: zona occludens-2; FXR: fanesoid X receptor; MVID: microvillous Inclusion Disease; MYO5B: myosinVB protein; RAB11A: RAS-related protein RAB11 A; LT: liver transplantation; ESLD: end-stage liver disease; vitK: vitamin K; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutammyl transferase; AFP: alpha-1-fetoprotein; BA: bile acids.

[a] Alkaline phosphatase levels in pediatric population are strongly influenced by the levels of bone isoenzymes and are therefore not reported.

[b] MYO5 B is classified by OMIM, online mendelian inheritance in man, as the gene responsible for microvillus inclusion disease but not yet for PFIC6.

G. Vitale et al. / Digestive and Liver Disease

Non-progressive familial intrahepatic cholestasis				
	BRIC	ICP	DIC	LPAC
Locus/gene/protein	18q21-22/ATP8B1/FIC1 2q24/ABCB11/BSEP 18q21.1/MyosinVB/MYO5B	18q21-22/ATP8B1/FIC1 2q24/ABCB11/BSEP 7q21/ABCB4/MDR3 9q21.11/TJP2/Z0-2 12q23.1/NR1H4/FXR	2q24/ABCB11/BSEP 7q21/ABCB4/MDR3	7q21/ABCB4/MDR3
Clinics	Intermittent severe cholestasis (intervals weeks to years); hearing loss, pancreatitis, diarrhea	Transient cholestasis + itching during pregnancy; post-natal resolution; potentially serious fetal complications	Chronic liver injury; acute hepatitis; fulminant hepatic failure Use of herbal remedies and naturopathic substances should be investigated; Onset < 1-12 months by drug adiministration	<40y cholelithiasis; intrahepatic microlithiasis; recurrence of biliary symptoms after cholecystectomy; previous episodes of ICP; familial history of gallstones
Laboratory				
BA	High during attack	High during pregnancy	Normal or mild elevation	High during obstruction
GGT	Low or normal	Normal or mild elevation	Variable	High
ALP	High	Normal or mild elevation	High	Normal to high
AST/ALT	Normal or mild elevation	Normal or mild elevation	Moderate or severe elevation	Normal or mild elevation
AFP	No data	No data	No data	No data
Histology	Centrolobular cholestasis, no alterations of liver structure, no BSEP tissue expression	Not performed	Loss of BSEP/MDR3 expression, canalicular cholestasis, hepatocellular inflammation	Not required; imaging based diagnosis

BRIC: benign recurrent intrahepatic cholestasis; ICP: intrahepatic cholestasis of pregnancy; DIC: drug induced cholestasis; LPAC: low-phospholipid-associated cholelithiasis; BSEP: biliary salt export pump; MDR-3: class III multidrug resistance P-glycoprotein; TJP-2: tight junctions protein-2; zo-2: zona occludens-2; FXR: fanesoid X receptor; MYO5B: myosinVB protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutammyl transferase; ALP: alkaline phosphatase; AFP: alpha-1-fetoprotein BA: bile acids.

Benign rekürren intrahepatik kolestaz

Otozomal resesif geçişli intermitan şiddetli kolestaz ile karakterizedir.

BRIC-1'de ATP8B1 geninde, BRIC-2'de ise ABCB11 geninde mutasyon mevcut.

Hamilelik, enfeksiyonlar veya oral kontraseptifler gibi ilaçlar kolestaz ataklarını tetikleyebilir.

Benign rekürren intrahepatik kolestaz

TANI KRİTERLERİ:

- En az iki kolestaz epizodu (birkaç aya veya yıla kadar asemptomatik dönem)
- İntrahepatik kolestazı düşündüren laboratuvar testleri
- Kolestazın neden olduğu şiddetli kaşıntı
- Kolanjiyografide normal intra ve ekstrahepatik safra kanalları
- Sentrilobüler kolestazı düşündüren karaciğer histolojisi
- Diğer kolestaz nedenlerinin yokluğu

Olgunun İzlemi

TÜRK KARACİĞER ARAŞTIRMALARI DERNEĞİ

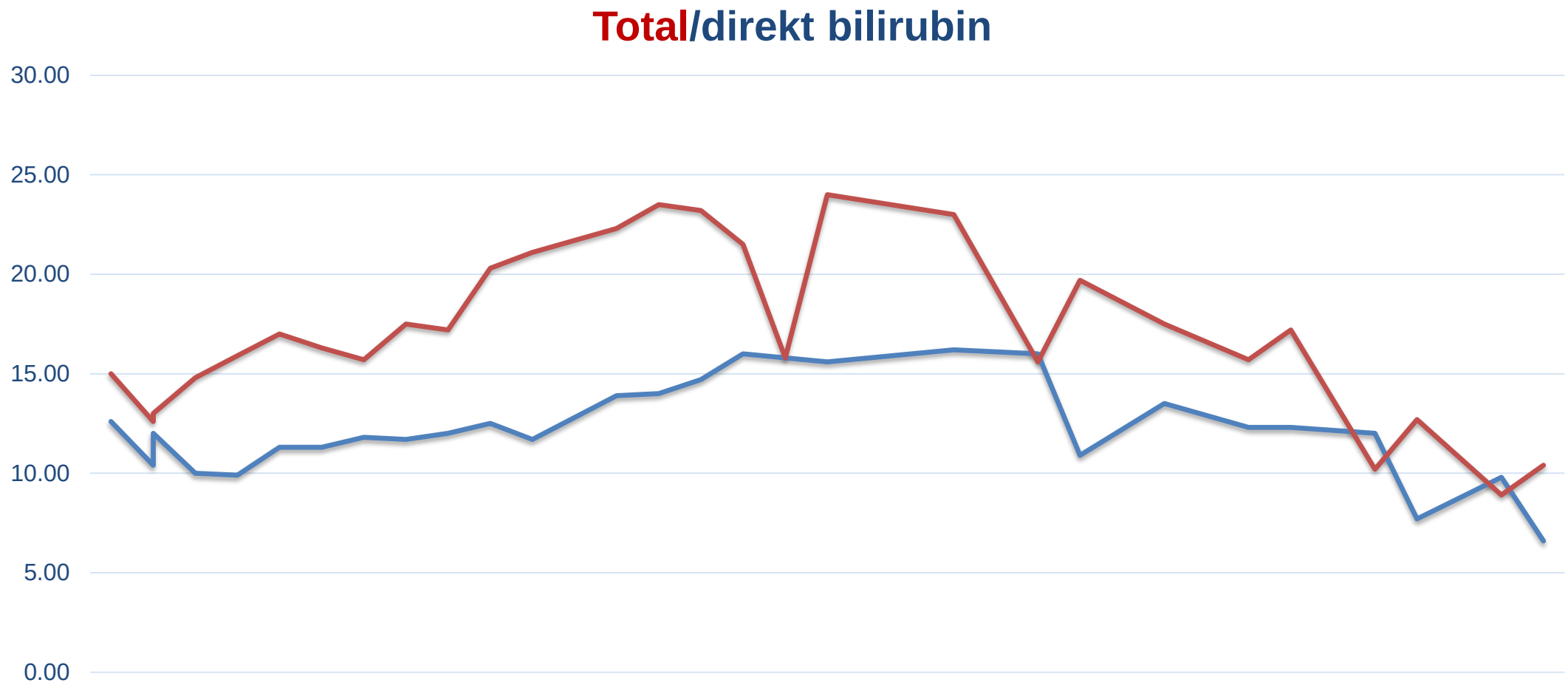


Table 1. — **Summary of BRIC case reports reporting at least one potential trigger factor from 1959-1988**

Case	Reference	Year	Sex	Age (y)	Age at 1st episode	nb of episodes	Trigger factor	Genetic Defect	Extrahepatic complication	Nb of attack per month	Longest episode	FH of cholestasis
1	Summerskill and Walshe [1]	1959	F	29	9 y	5	pregnancy(a) x1 influenza x1	NA	NA	Mar x1 Oct x1 Sep x2	2 y	NA
2	Stark [20]	1967	F	NA	17 m	9	Otitis media x2	NA	NA	NA	6 m	NA
3	Lesser [21]	1973	F	23	20 y	2	OCPs / tetracycline	NA	NA	Oct x1	7 w	Brother
4	Lesser	1973	F	46	21 y	13	Pregnancy x5 Viral illness x1 OCPs x2 Flu vaccine x1	NA	NA	NA	7 m	Sister
5	De pagter et al [22]	1976	F	11	1 y	NA	Viral illness x?	NA	NA	NA	3 w	Sister
6	De pagter et al	1976	F	53	14 d	<8	Pregnancy x1	NA	Gallstones	NA	2 y	Father's family
7	De pagter et al	1976	M	41	6 y	<3	Tonsillitis x1	NA	NA	NA	NA	Sister
8	Summerfield et al [17]	1980	M	51	18 y	11	Viral illness x?	NA	Gallstones	NA	3 m	NA
9	Summerfield et al	1980	M	66	28 y	5	URTI x2 (UTI x1 and Sulfonamides)	NA	Gallstones	NA	3 m	NA
10	Cohen et al [23]	1985	F	58	48 y	4	Tonsillitis x2	NA	NA	NA	4 m	NA

Pregnancy(a): during first 2 trimesters NA: data not available; F: female; M: male; y: year; d: day; w: week; m: month; URTI: upper respiratory tract infection; UTI: urinary tract infection; OCPs: oral contraceptive pills; x: number of times; Nb: number; FH: family history; ?: unknown; Mar: March; Oc t: October; Sep: September.

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Table 2. — **Summary of BRIC case reports reporting at least one potential trigger factor from 1989-2011**

Case	Reference	Year	Sex	Age (y)	Age at 1st episode	Nb of episodes	Trigger factor	Genetic Defect	Extrahepatic complication	Nb of attack per month	longest episode	FH of cholestasis
11	Lau et al [24]	1989	F	15	11 y	5	Influenza x2	NA	NA	Aug x1	6 m	Brother
12	Bijleveld et al [16]	1989	M	7	1 y	2	Gastroenteritis x1	NA	NA	NA	6 m	Brother
13	Brenard et al [25]	1989	F	25	NA	2	Pregnancy(a) x1	NA	NA	NA	7m	NA
14	Brenard et al	1989	F	46	NA	7	Pregnancy (a) x1	NA	NA	NA	4 m	Sister
15	Brenard et al	1989	F	30	NA	3	Pregnancy (b) x1	NA	Gallstones	NA	4 m	NA
16	Brenard et al	1989	F	37	NA	8	Pregnancy (a) x1	NA	Gallstones	NA	15m	NA
17	Brenard et al	1989	F	23	NA	3	Pregnancy (a) x1	NA	NA	NA	12m	Brother
18	Brenard et al	1989	F	48	NA	2	Pregnancy(a) x1	NA	NA	NA	2 m	NA
19	Bijleveld et al	1989	M	14	8 y	9	Gastroenteritis x1	NA	NA	Nov x2/ Dec x2/ Jan x4 / Feb x1	6 m	Brother
20	Lovisetto et al [26]	1990	F	42	5 y	10	Pregnancy (a) x1	NA	Gallstones	NA	NA	Brother
21	Al drees et al [27]	1999	F	11	4 y	3	Viral illness x1	NA	NA	NA	8 w	NA
22	Kubitz et al [28]	2006	M	17	3 m	5	URTI x1 Viral illness x3	BSEP	NA	NA	8 w	NA
23	Ermis et al [29]	2010	M	23	11 y	3	URTI x1	ATP8B1	NA	NA	6 w	NA
24	Beausejour et al [30]	2011	F	NA	NA	2-3	URTI x? OCPs x?	BSEP	Pancreatitis x1	NA	18 m	Sister
25	Beausejour et al [30]	2011	F	NA	9 m	2-3	URTI x? OCPs x?	BSEP	NA	NA	1.5 y	Sister

Pregnancy (a): during first 2 trimesters; Pregnancy (b): during third trimester. NA: data not available; F: female; M: male; y: year; w: week; m: month; URTI: upper respiratory tract infection; OCPs: oral contraceptive pills; x: number of times; Nb: number; FH: family history; ?: unknown; Aug: August; Feb: February; Jan: January; Dec: December; Nov: November.

Table 3. — **Summary of BRIC case reports reporting at least one potential trigger factor from 2012-2020**

Case	Reference	Year	Sex	Age (y)	Age at 1st episode	Nb of episodes	Trigger factor	Genetic Defect	Extrahepatic complication	Nb of attack per month	longest episode	FH of cholestasis
26.	Folvik et al [10]	2012	M	42	27 y	10	URTI x5	ATP8B1	Pancreatitis x2	Jan x1	12 w	Twin
27.	Folvik et al	2012	M	62	41 y	12	Pneumonia x1 vs erythromycin	NA	NA	NA	8 m	NA
28.	Folvik et al	2012	M	21	15 y	7	Havrix x2	ATP8B1	Pancreatitis x2	Decx1/ June x1/ July x1 /April x1/ Sept x1 May x1 /March x1	14 w	NA
29.	Mizuochi et al [31]	2012	F	7	7 y	1	Influenza x1	ATP8B1	NA	NA	2 y	NA
30.	Moghadamrad et al [32]	2013	F	44	44 y	1	Gastroenteritis x1 vs acetaminophen	BSEP	gallstones	NA	NA	Grand mother and aunt
31.	Urszula et al [33]	2014	M	14	14 y	3	Tetracycline vs skin infection x1	ATP8B1	NA	NA	3 m	NA
32.	Schreiner et al [34]	2019	M	16	16 y	3	Tonsillitis x2 vs cefuroxime/ amoxicillin-clavulanic acid	BSEP	NA	NA	NA	NA
33.	Halawi et al [35]	2020	F	37	3 m	8	Pregnancy x1 Pneumonia x1 Hyperthyroidism x1	ATP8B1	Pancreatitis x1	Feb x1	5 m	NA
34.	Arthur et al [36]	2020	F	27	24 y	3	Pregnancy x1	BSEP	NA	NA	NA	NA
35.	Salyani et al [37]	2020	M	21	14 y	6	Skin infection x2	NA	NA	Dec x1 April x1 June x2	8 w	NA

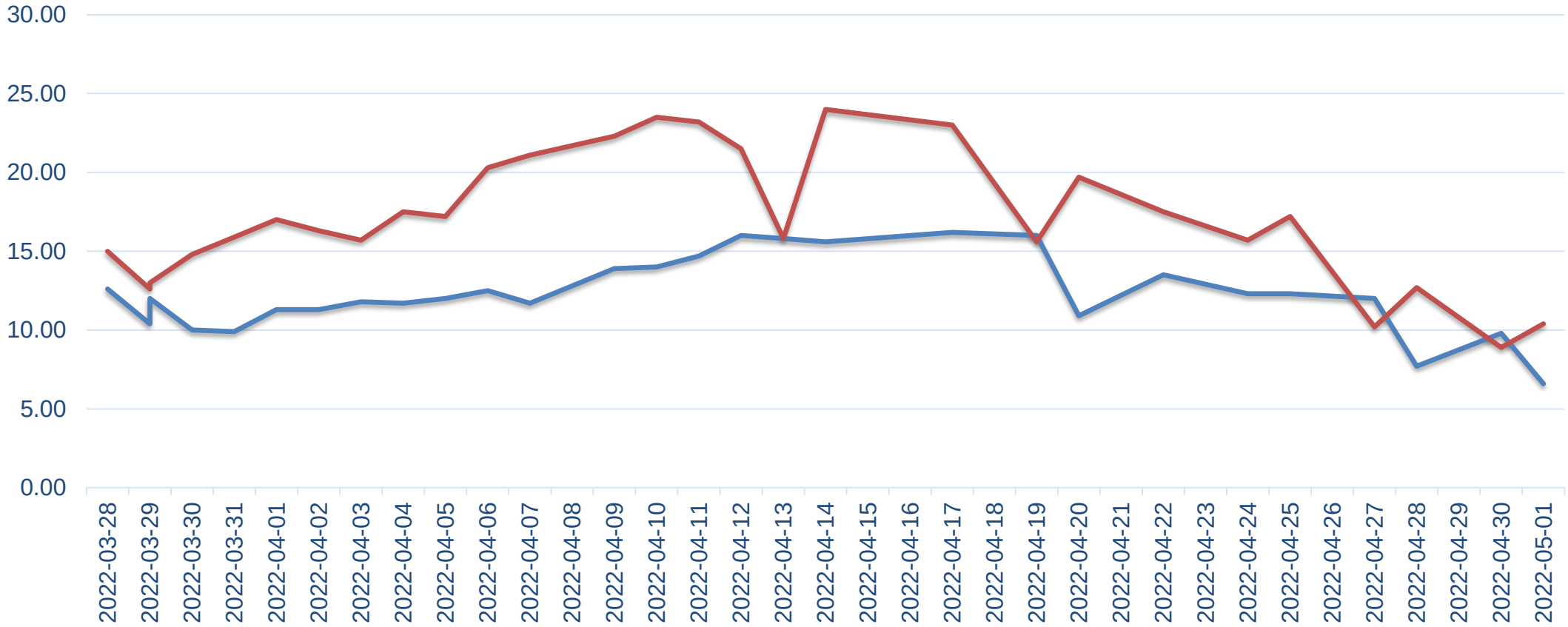
NA: data not available; F: female; M: male; y: year; w: week; m: month; URTI: upper respiratory tract infection; OCPs: oral contraceptive pills; x: number of times; Nb: number; FH: family history; ?: unknown; Dec: December; Apr: April; Feb: February; Sept: September.

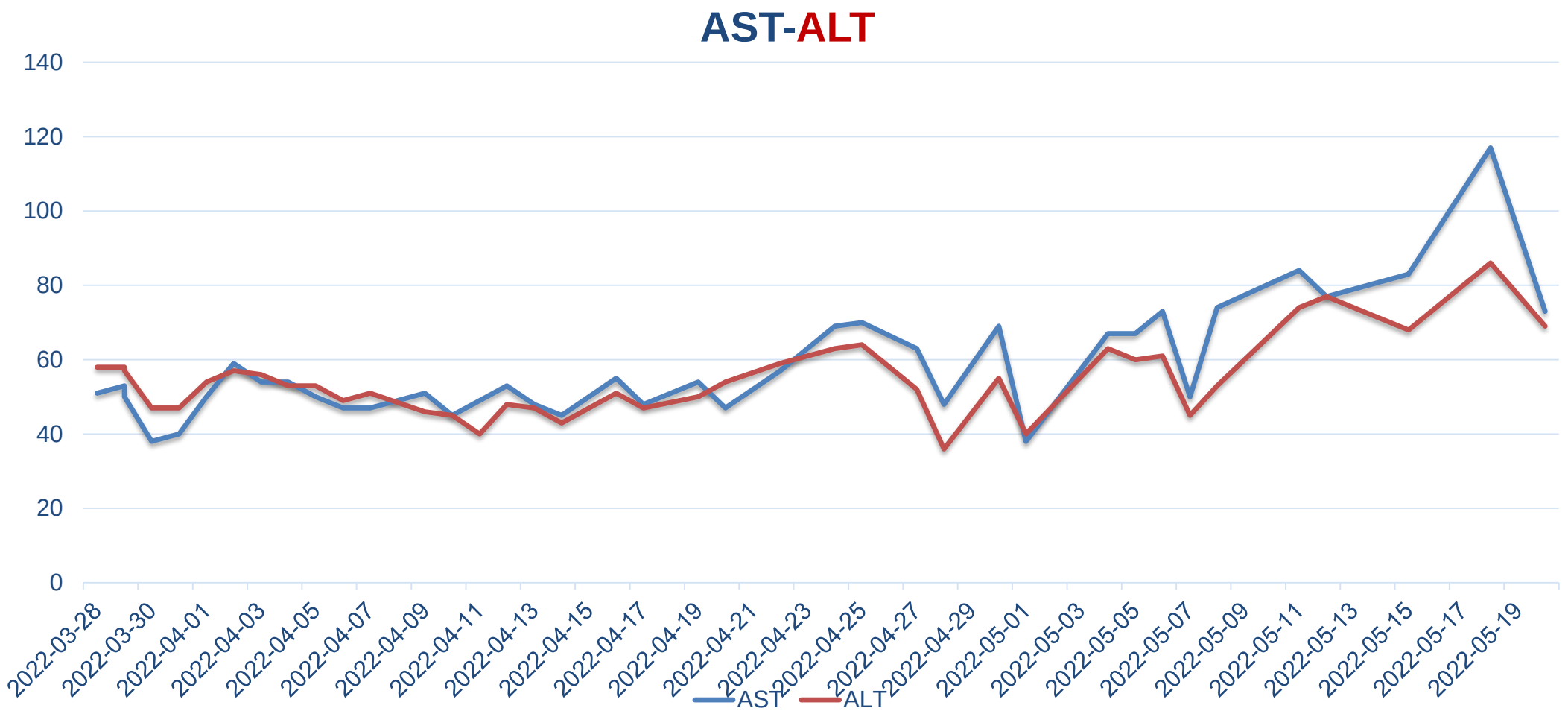
Table 4. — **Summary of variables presented in table 1-3**

Sex	Mean number of episodes (SD)	Mean age at presentation (SD)	Genetic defect	Extrahepatic complication	Mean age at first episode(range)	Season	Mean Duration of longest episode (range)	Presence of family history
F:62.9% M:37.1%	5.31±3.42	31.47±16.82	BSEP: 6x ATP8B1:6x	Pancreatitis:6x Gallstones:6x	14.28 (3m-48y)	Winter: 11x Autumn:6x Spring:5x Summer:4x	32.37% (3m-2y)	42.8%

F: female; M: male; SD: standard deviation; x: number of time; m: month; y: year.

Total/direkt bilirubin




AST-ALT
140
120
100
80
60
40
20
0
2022-03-28
2022-03-30
2022-04-01
2022-04-03
2022-04-05
2022-04-07
2022-04-09
2022-04-11
2022-04-13
2022-04-15
2022-04-17
2022-04-19
2022-04-21
2022-04-23
2022-04-25
2022-04-27
2022-04-29
2022-05-01
2022-05-03
2022-05-05
2022-05-07
2022-05-09
2022-05-11
2022-05-13
2022-05-15
2022-05-17
2022-05-19
AST
ALT