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Pearls on Underwriting Liver Disease including Hep B, Hep C, Alcoholic and Fatty Liver Disease

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AGENDA

- Epidemiology Of Our Top Liver Conditions
- Liver Biopsy: Historical Review
- Predicting Cirrhosis Without Liver Biopsy: Red Flags at the bedside!
- FibroSure/FibroTest and HepaScore/FibroScore
- FibroScan
- Underwriting Risks for Hep B, Hep C, ALD and NAFLD using Noninvasive Testing
- Case Studies

Top Liver Conditions in Developed Countries

- Chronic viral hepatitis (B and **C**) – increase in Hep C related to IV heroin on rise
- Alcoholic liver disease
- Hemochromatosis (iron overload)
- Nonalcoholic fatty liver disease (NAFLD)

Less common causes:

Autoimmune hepatitis, Primary and secondary biliary cirrhosis, Primary Sclerosing Cholangitis, Wilson, Alpha 1 antitrypsin deficiency, Celiac, Granulomatous liver disease, Polycystic liver diseases, Infection (brucellosis, syphilis, echinococcosis), Right heart failure, Osler Weber, veno-occlusive disease

Top Liver Conditions in Developing Countries

- Highest burden is Hepatitis B via vertical transmission Mother to Child
- Hepatitis E especially in Africa and Asia from contaminated waters
- Concomitant HIV with or without Hep B or C
- Alcoholism
- Aflatoxin (carcinogen) especially in sub-Saharan Africa and China
- Liver cancer is most common cause of cancer in men in 11 developing countries: Mongolia, Gambia, Thailand, South Korea, Taiwan, North Korea, Guinea, Mali, Cameroon, Tonga and Guinea-Bissau (in order of most to least)
- Liver flukes-Clonorchiasis – high association with cholangiocarcinoma

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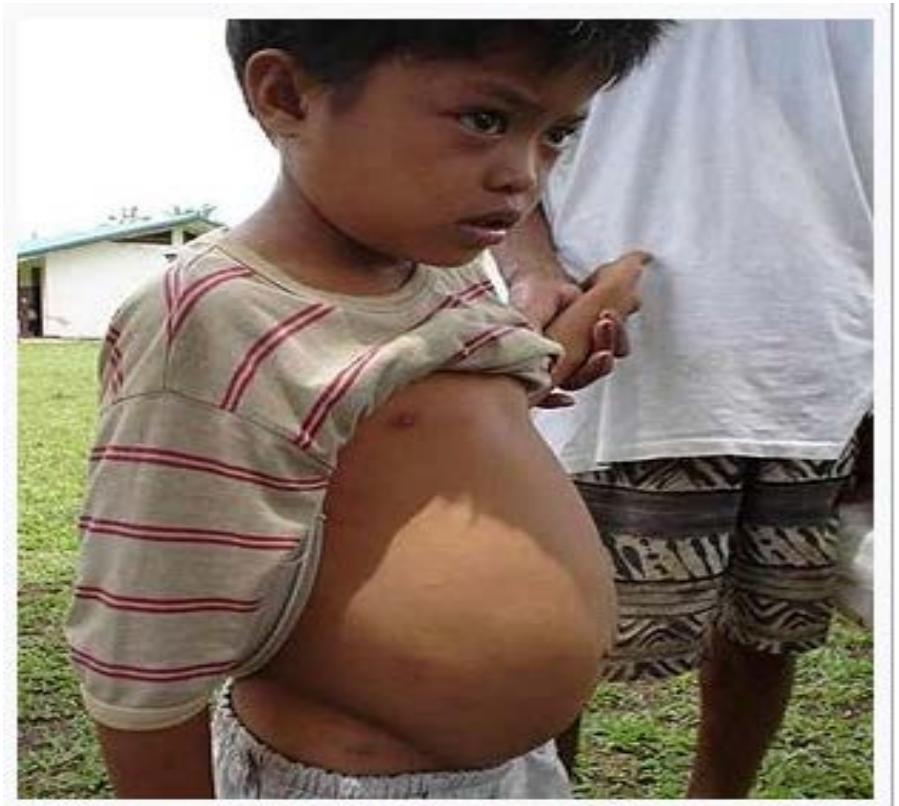
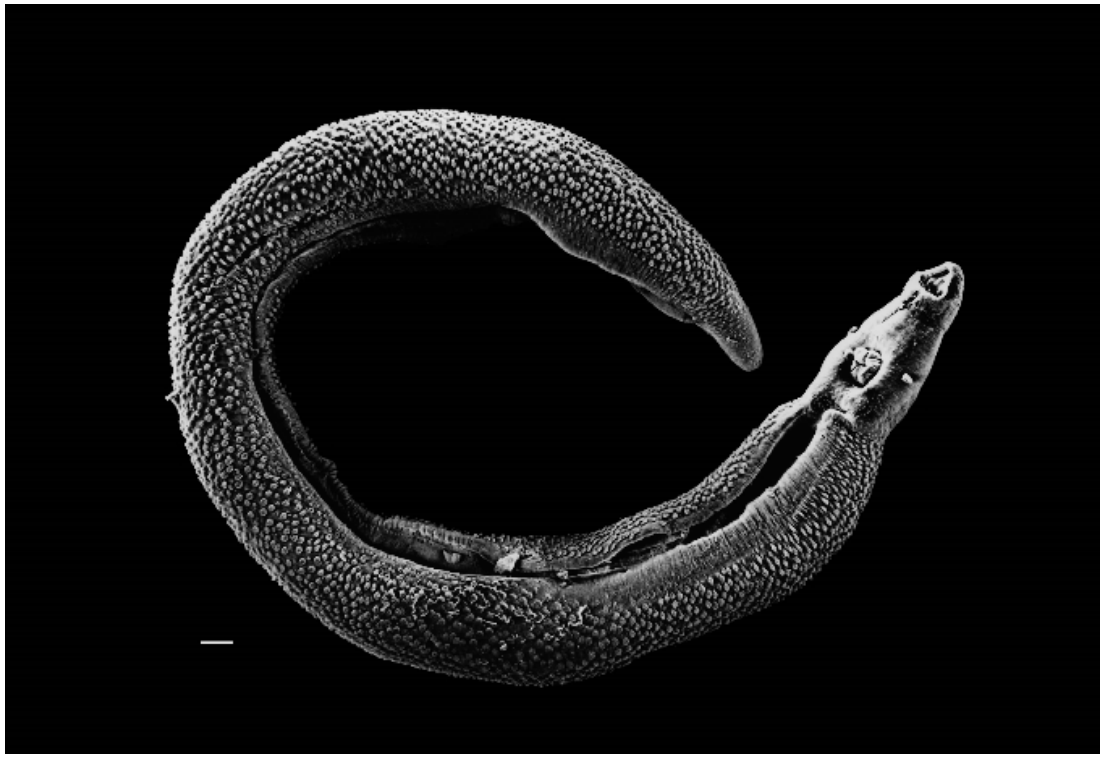
Schistosomiasis: Common Cause of Liver Disease
Snail Fever

Ascites



11-year-old boy with abdominal fluid and portal hypertension due to schistosomiasis (Agusan del Sur, Philippines)

Parasitic flatworm: Schistosome



Prevalence of Hepatitis B

- Estimated 350 million worldwide have Chronic Hep B
- 2 Billion are infected at some point in their life
- Most prevalent in Western Pacific and Africa in which 6% of population infected; South-East Asia, China, Taiwan, Sub-Saharan Africa and the Amazon basin with prevalence up to 60%; Rates falling with increased Hep B vaccination
- Those at risk for **chronic** disease: depends mostly on age at which infected

In infants and children: 80-90% of infants infected during the first year of life

30-50% of children infected before age 6

In adults: Less than 5% of otherwise healthy persons infected

Concern is 20-30% of adults with chronic Hep B will develop cirrhosis and/or liver cancer

Data from EASL Paris 2018 Liver Congress

Prevalence of Hepatitis C

- HCV most widespread transmissible disease globally, infecting 185 million people worldwide (3% of world population) of which 71 million have Chronic Hep C
- 14-45% spontaneously clear the virus within 6 months
- UK National HCV database: 1/3 of those < 18 yrs old have HCV (53% by IV drug use)
- Egypt had highest prevalence with estimated 40,000 death per year; 10% between ages 15-59 have chronic hep C - prevalence declining as that group infected from mass schistosomiasis treatment dies off
- Baby boomers born between 1945-1965 make up 75% of cases of Hep C per CDC in USA
- Why Baby Boomers?

  1970-1980 highest rates of Hep C

  Non A/non B Hep not isolated in blood products until 1992

  Universal precautions were not implemented until 1990s
- HCV the silent pandemic

Stats from EASL Amsterdam liver congress April 2017

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Prevalence of NAFLD and NASH

- NAFLD has doubled over last 20 yrs, affecting 20% of world population
- 34% of Americans
- Associated with obesity and DM and together are considered #1 cause of liver disease in Western countries
- Estimated from 2 large European studies that 43-70% with DM type 2 have NAFLD (EASL Amsterdam Liver Congress 2017)
- Estimated up to 10% of American children have NAFLD per CDC
- 10-30% with NAFLD have NASH
- 6 million estimated in USA have NASH
- 25% of those with NASH have cirrhosis

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Prevalence of ALD

- Most prevalent cause of advanced liver disease in Europe
- Estimated 10-35% of alcoholics have ALD
- Common for those with ALD to share other risk factors such as NAFLD or chronic viral hepatitis
- Synergy with combination of HCV and alcohol: Cohort study found 30 fold increase in cirrhosis w/heavy ETOH and post transfusion Hep C

Per EASL Barcelona 2016

What Increases Risk of ALD?

Increase risk for cirrhosis if >60 gm/day for > 10 yrs in men and >20 gms/day in women. Yet only 6-41% develop cirrhosis.

Denmark found drinking beer and spirits over wine was a factor in ALD (per survey of 30,000)

Drinking outside of meal times increases risk of ALD by almost 3 fold

Binge drinking: Defined as > 5 drinks in men and > 4 in women in 2 hour period

Protein calorie malnutrition – mortality directly proportional to degree of malnutrition with up to 80% mortality with severe malnutrition (< 50% of normal nutritional intake)

Prevalence of Liver Cirrhosis

- Globally, estimated one million deaths in 2010

  equates to 2% of all deaths worldwide d/t cirrhosis

- Most liver transplants are for those with histories of ALD and Hep C

Pathophysiology of Cirrhosis

Two Primary Ingredients

Hepatic Fibrosis

Hepatocellular Damage

↓

Activate Kupffer cells, thrombocytes, hepatic stellate cells

↓

Differentiate to myofibroblasts and proliferate

↓

Synthesis and accumulation of extracellular matrix

↓

Fibrosis

Regenerating Liver Cells

Cytokines – Epithelial growth factor– hepatocyte growth factor--Tumor necrosis factor

↓

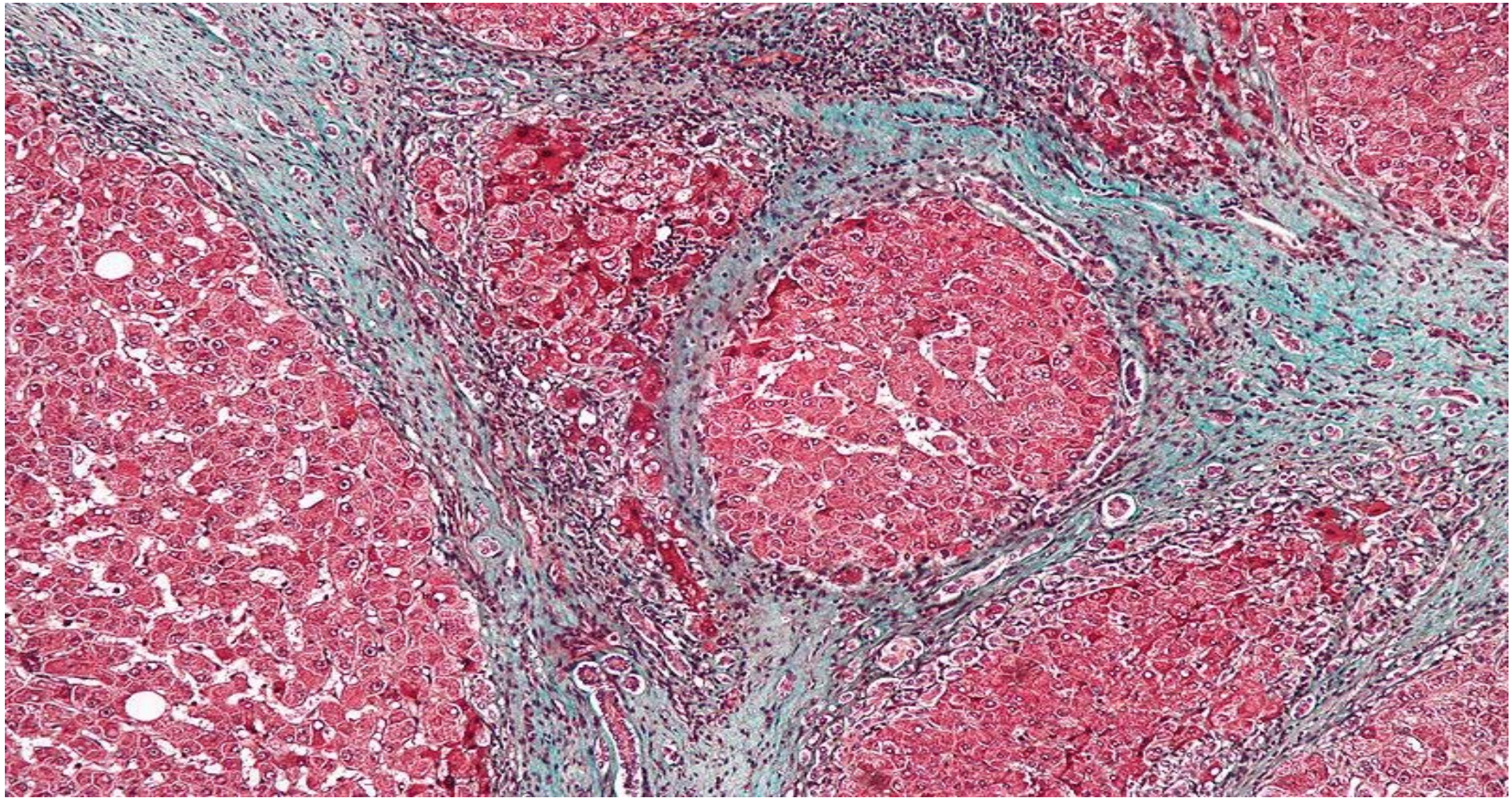
Hepatocellular Hyperplasia and Angiogenesis

↓

Regenerating Nodules

Venous drainage cannot accommodate the additional blood volume and the regenerating nodules compress hepatic venules, all contributing to portal vein pressure to increase

Histology of Liver Cirrhosis



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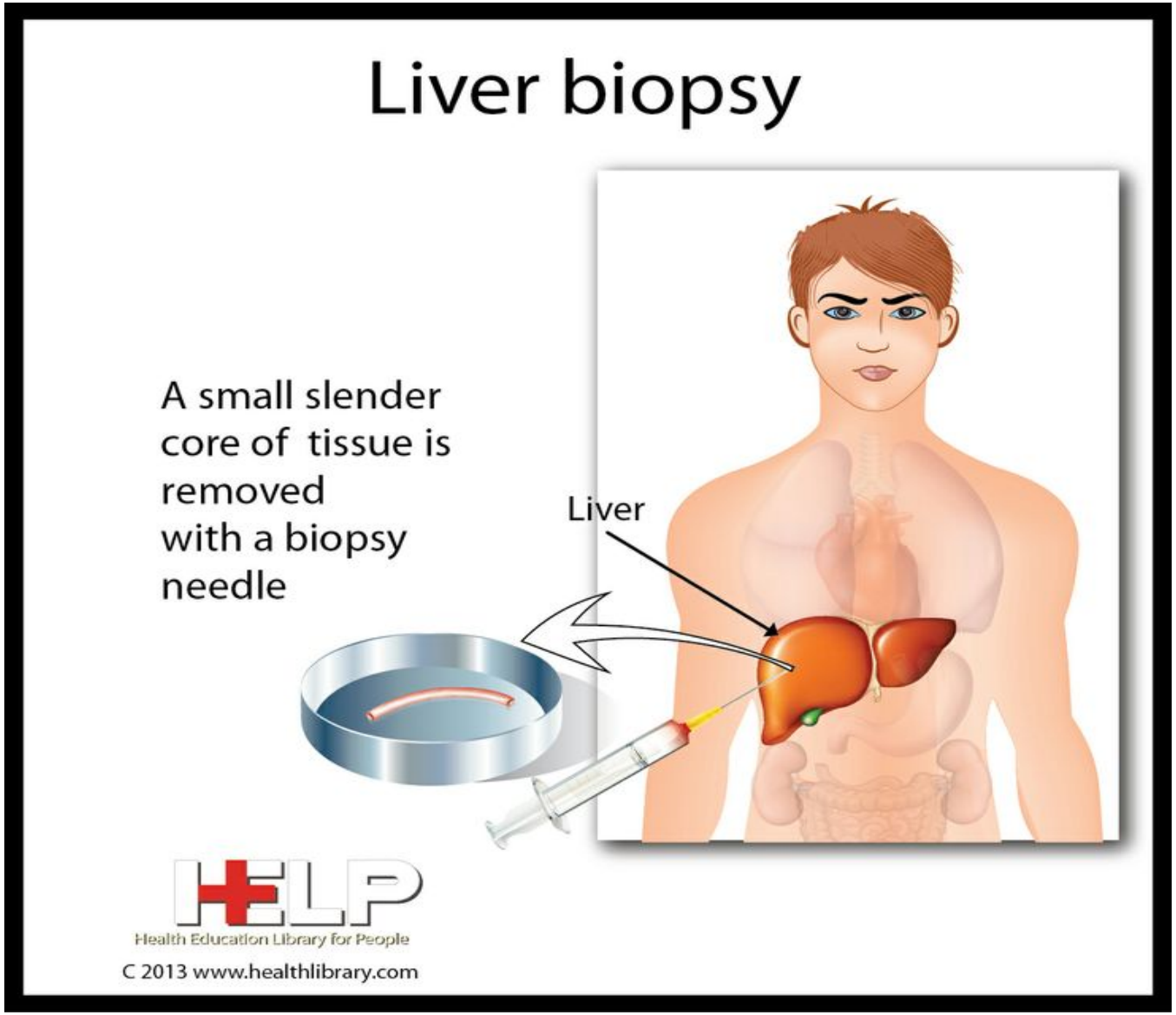
Gold Standard
(Past tense, in my opinion)

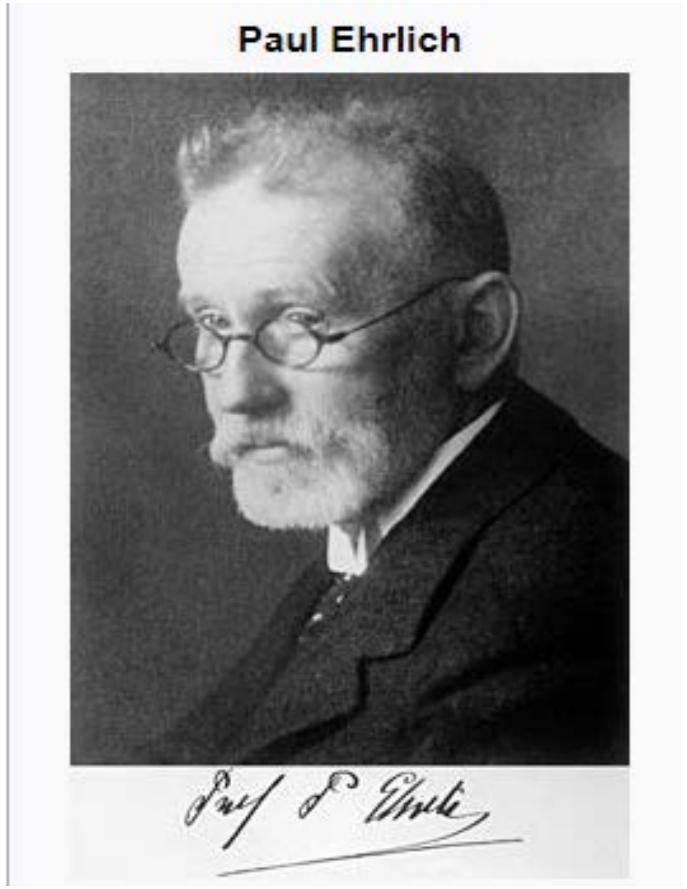
First liver aspirate performed by German physician: Paul Ehrlich in 1883

Reportedly, first liver biopsy performed percutaneously in 1920s



Let's digress a bit: Paul Ehrlich, M.D

Awarded Nobel Prize in Physiology and Medicine 1908 for work on Immunity



- Was into cell staining. Termed "MAST cell" from the German word Mast, a fattening feed for cattle
- Using alkaline, acidic dyes and creating neutral ones, could differentiate lymphocytes and leukocytes. Created basis to systematize leukemias.
- Studied RBCs subdividing into normoblasts, megaloblasts, poikiloblasts - laying down the basis for anemias.
- Discovered first drug to target syphilis: Salvarsan
- Methylene Blue and Malaria
- Magic Bullet…Targeting a pathogen by concept of antibody-drug conjugation

Liver Biopsy Cons and Complications

- Expensive: if not insured, cost range $2000-$7000 USD
- Requires half day or short stay in hospital
- Associated with pain (20%) and bleeding (1%)
- Death reported 1/10,000 biopsies
- Only small piece of liver (1/50,000th)– can lead to sampling error and incorrect staging: under-staging in up to 25-30% of liver biopsies
- Interpreted by different pathologists can result in discrepancies in staging

Liver Biopsy Indications

Liver biopsy: degrees of indication for establishing the diagnosis, for staging and/or prognostication, and for treatment planning

	Diagnosis	Staging/Prognosis	Treatment
Hepatitis B	–-	+++	++
Hepatitis C	–-	+++	+++
Autoimmune hepatitis	+++	+++	+++
Primary sclerosing cholangitis	+++	+++	–-
Primary biliary cirrhosis	++	+++	+
Overlap syndrome	+++	+++	++
Nutritional-toxic/alcoholic steatohepatitis	+	+++	+
NAFLD/NASH	+++	+++	+
Iatrogenic-toxic	+++	+	+
Hemochromatosis	+++	+++	+++
Wilson's disease	+++	+++	–-
A1AT deficiency	+	++	–-
Acute liver failure	+++	+++	–-
S/p liver transplantation(rejection, re-infection)	+++	++	+++
Tumor:			
HCC	++	---	---
LCA	+++	---	+++
Metastases	+++	---	---

--- = irrelevant

+ = occasionally relevant

++ = usually relevant

+++ = highly relevant

Classification of Liver Histology

- Grade – Inflammation
- Stage - Fibrosis

Liver Biopsy Grading and Staging

Comparative Scoring Systems for Histologic Grade (Inflammation)		
IASL	**Batts-Ludwig**	**Metavir**
Minimal chronic hepatitis	Grade 1	A1
Mild chronic hepatitis	Grade 2	A1
Moderate chronic hepatitis	Grade 3	A2
Severe chronic hepatitis	Grade 4	A3

Comparative Scoring Systems for Histologic Stage (Fibrosis)			
Score	**IASL**	**Batts-Ludwig**	**Metavir**
0	No Fibrosis	No Fibrosis	No Fibrosis
1	Mild fibrosis	Fibrous portal expansion	Periportal fibrotic expansion
2	Moderate fibrosis	Rare bridges or septae	Periportal septae (> 1 septum)
3	Severe fibrosis	Numerous bridges or septae	Portal-central septae
4	Cirrhosis	Cirrhosis	Cirrhosis

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Key Points On Liver Biopsy

- The indications for biopsy must be weighed against the risk of complications
- Liver biopsy - means of securing the initial diagnosis of **autoimmune diseases including AIH, PSC, mixed forms of both AIH and PSC (overlapping syndrome) and PBC**
- Among all diagnostic methods for hepatic nodules, liver biopsy has the greatest sensitivity and specificity with respect to **determination of malignancy**
- Liver bx not necessary if clinical, labs and radiologic data strongly suggest the presence of cirrhosis or results do not alter the patient's management

How to Suspect Liver Cirrhosis w/o Biopsy

- Stigmata of chronic liver disease: physical exam findings
- Evidence of cirrhosis on lab or radiologic testing or by direct visualization while undergoing surgical procedure
- Evidence of decompensated cirrhosis: esophageal varices, ascites, spontaneous bacterial peritonitis or hepatic encephalopathy
- Meta-analysis found best ability to predict cirrhosis:

  Presence of ascites

  Platelet counts < 160K

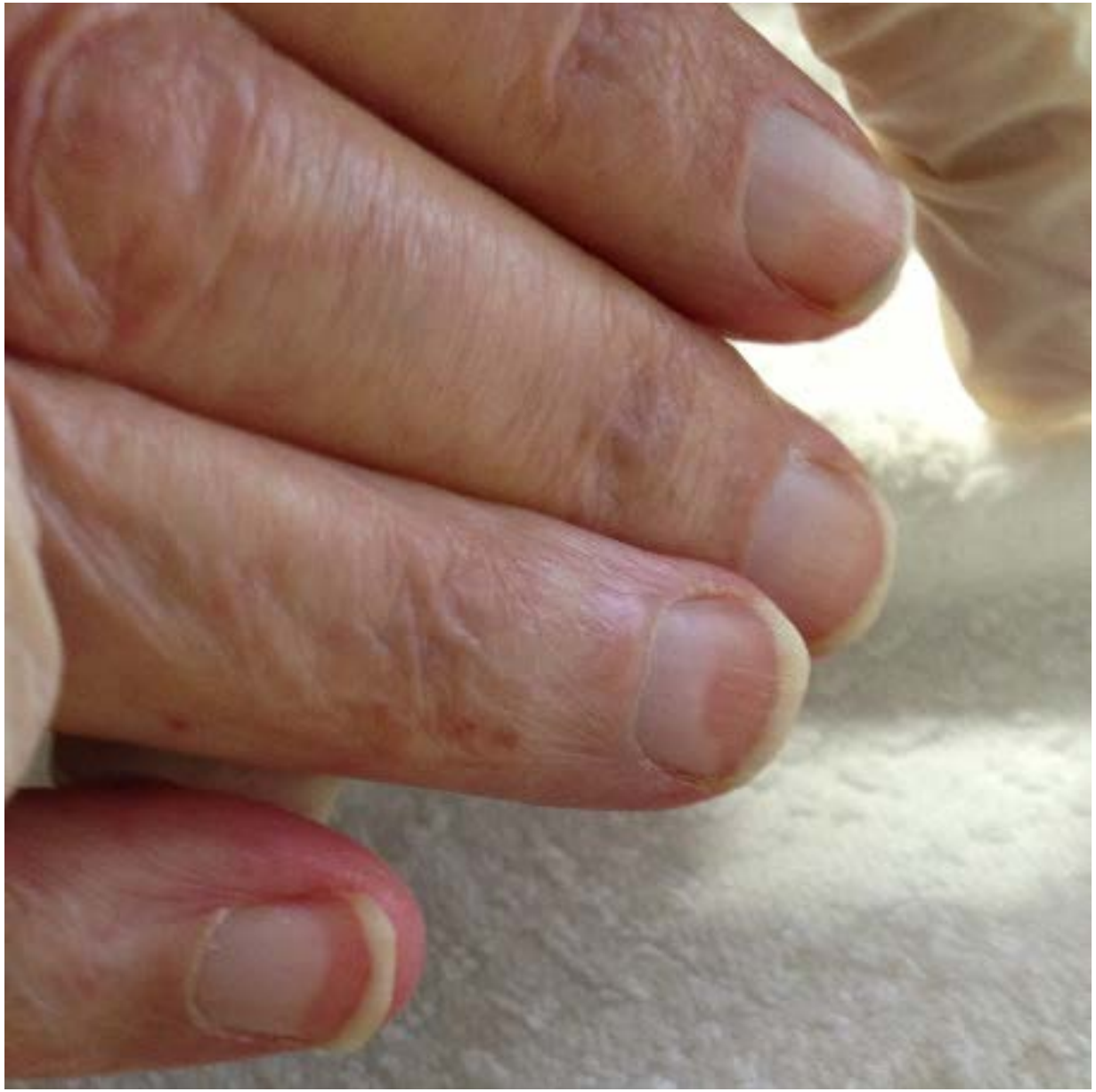
  Spider angiomas

  Bonacini cirrhosis discriminant score greater than 7

Stigmata of Liver Disease

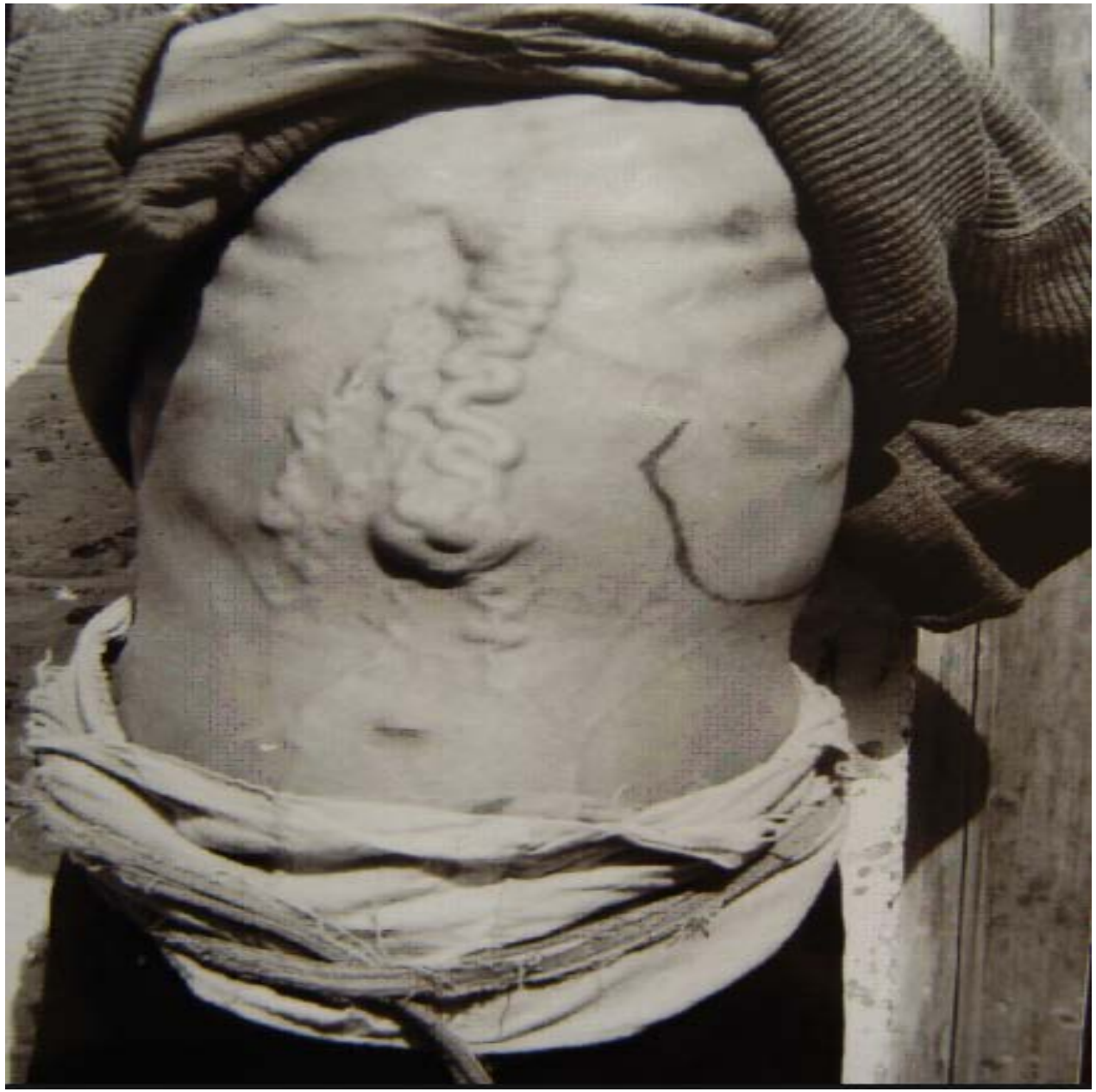
Physical Exam Findings

Terry’s Nails



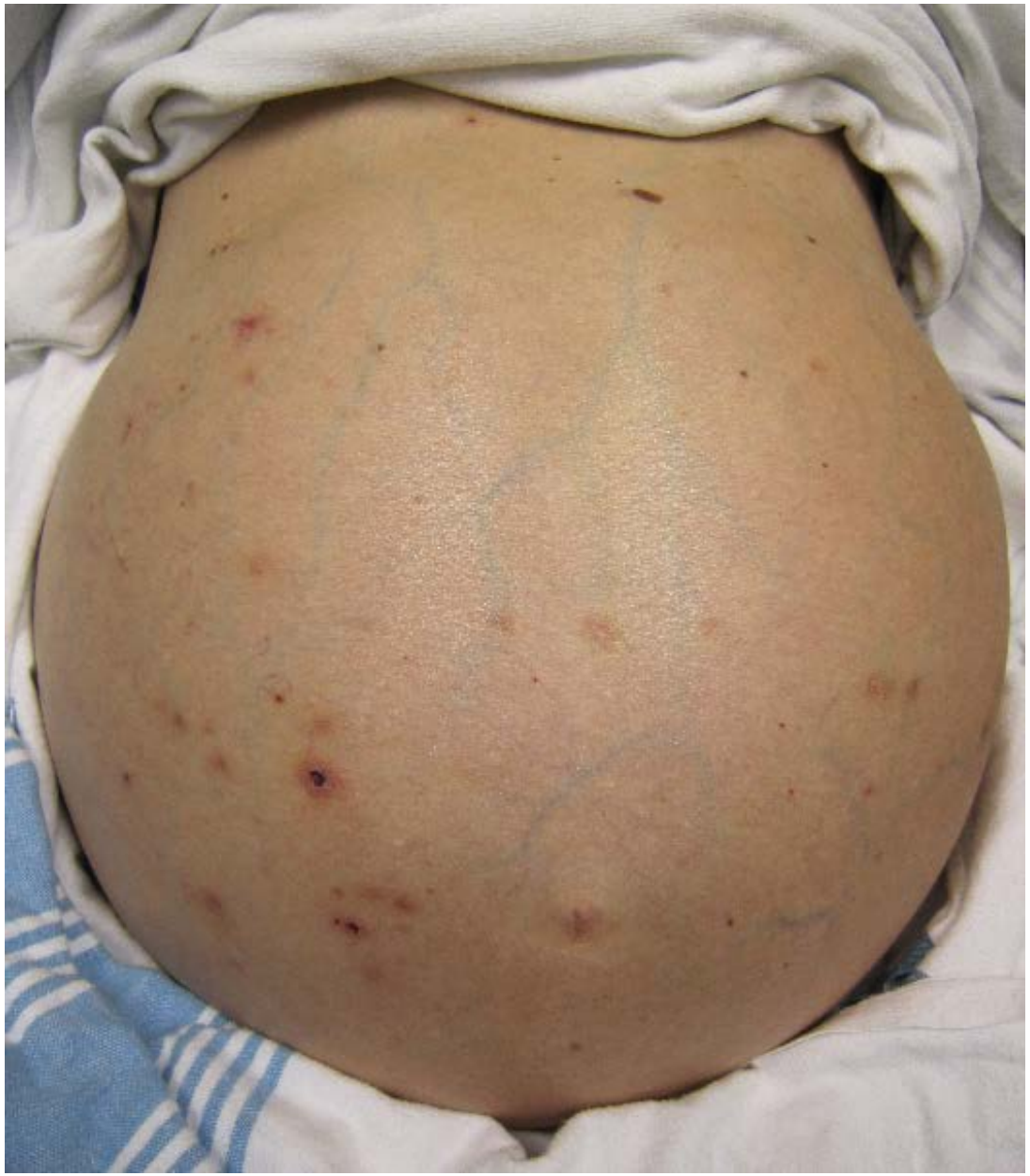
Pop Question: What sequela of cirrhosis does this depict?

Caput Medusa : distended abdominal veins

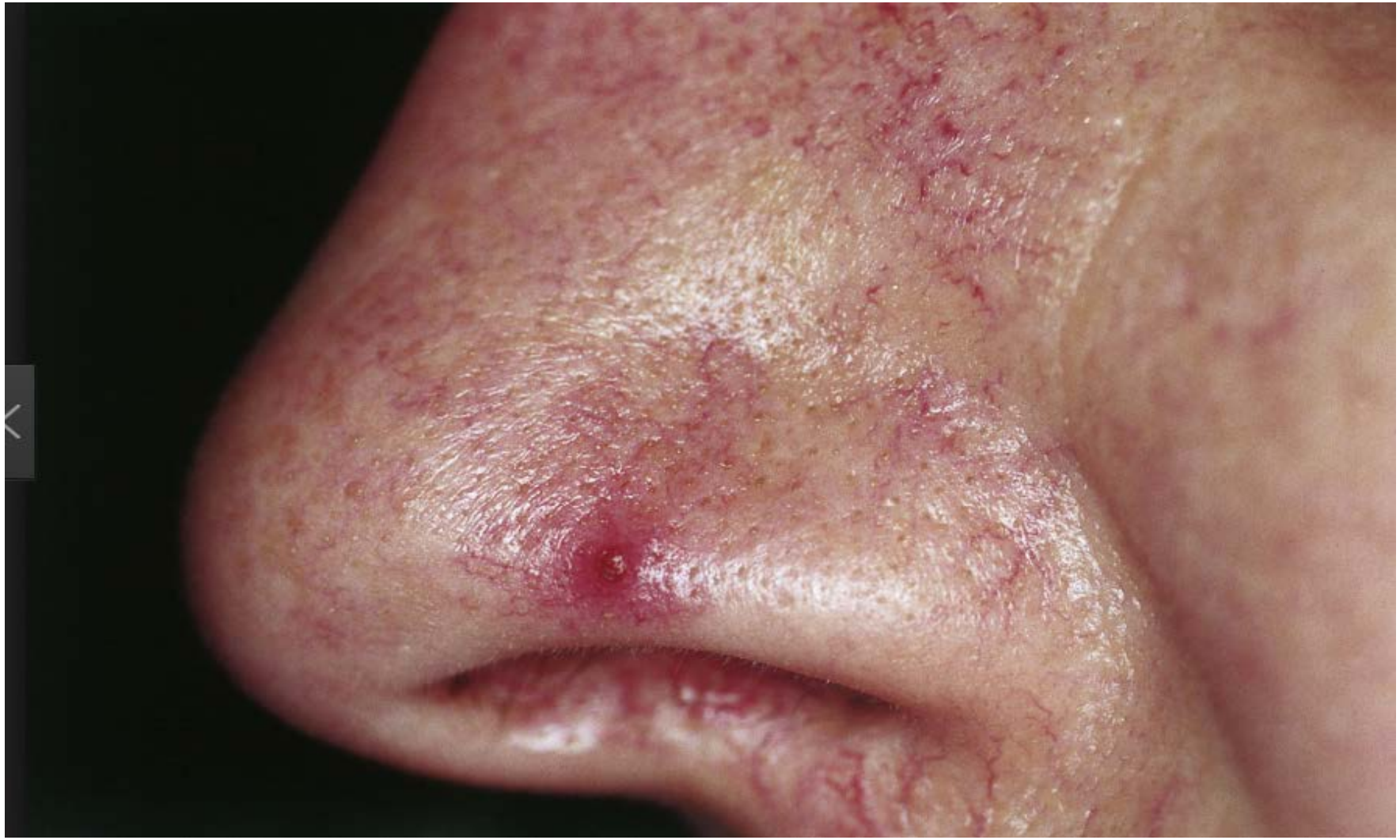


Can you guess which depicts gynecomastia due to liver cirrhosis

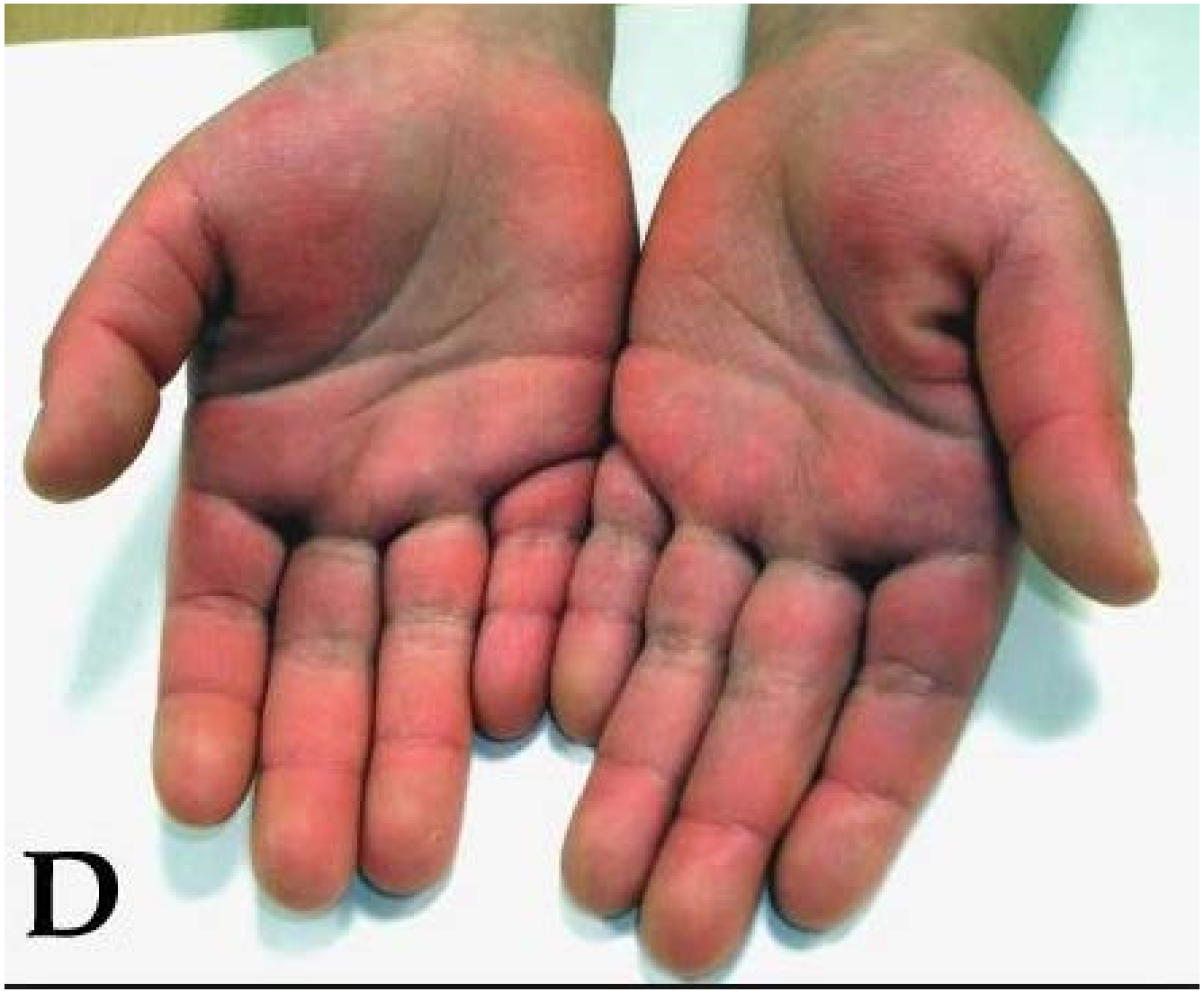
Ascites



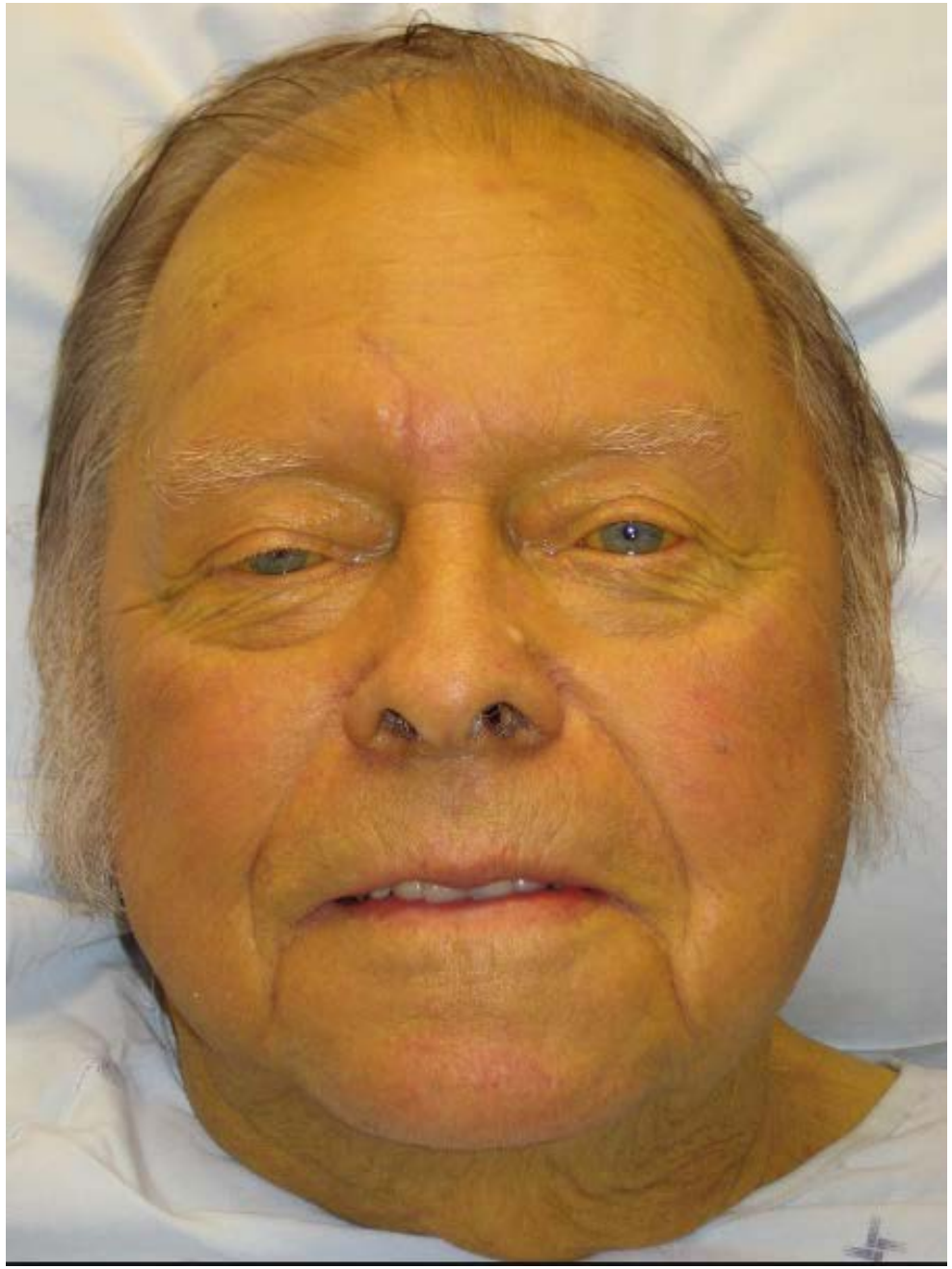
Spider Nevi or Facial Telangectasia



Palmar Erythema



Jaundice



Poem by William Bean, a physician from 19th century

An older Miss Muffett

Decided to rough it

And lived upon whisky and gin.

Red hands and a spider

Developed outside her –

Such are the wages of sin.

Bean studied spider nevi extensively and noted its association with alcoholic cirrhosis. He was a British physician of the 19th century

Now for the PEARLS to make your lives easier!!

52 yr old global business man with truncal obesity, social ETOH, ED, gynecomastia.

Labs:

- CBC nml (platelets 157K, Hgb/HCT 14.5/48, WBC 4.5)
- Insurance Labs: ALT 40, AST 58, GGT 65, albumin 3.8, HDL 75, nonreactive HepBSAg, nonreactive HepCAb
- RX: Spironolactone, Nexium and Viagra

That's all you have and this is enough info to provide an action.

Diagnostic Accuracy of Labs in Detecting Cirrhosis

Finding	Source	No. of Studies	Total No. of Patients	No. of Patients With Cirrhosis	Sensitivity	Specificity	Positive LR (95% CI)	I^2 %	P Value	Negative LR (95% CI)	I^2 %	P Value
Thrombocytopenia, platelet count, x 10^3/μL <110[a]	55, 60, 61, 85, 112, 113, 140	7	2533	1137	0.50	0.95	9.8 (2.6-17)	87	<.001	0.53 (0.35-0.71)	90	<.001
<160[a]	62, 65, 81, 96-99, 105-107, 110, 113, 115, 117, 119, 124, 126, 141	19	6670	1394	0.74	0.88	6.3 (4.3-8.3)	90	<.001	0.29 (0.20-0.39)	81	<.001
<200[a]	66, 67, 72, 78, 84, 113	6	2154	697	0.80	0.72	2.9 (1.7-4.1)	95	<.001	0.28 (0.07-0.48)	86	<.001
Prolonged PT/INR[a]	55, 60-63, 76-78, 81, 113, 117, 124	12	3418	1392	0.48	0.90	5.0 (3.2-6.9)	82	<.001	0.57 (0.39-0.75)	95	<.001
Albumin <3.5 g/dL[a]	55, 58, 60, 62, 81, 86, 103, 108	8	961	499	0.45	0.90	4.4 (1.5-7.3)	57	.02	0.61 (0.41-0.81)	79	<.001
AST>2 x ULN	72	1	179	20	0.65	0.80	3.2 (2.1-5.0)			0.44 (0.24-0.80)		
GGT>300 U/L	86	1	100	55	0.49	0.82	2.8 (1.4-5.5)			0.62 (0.46-0.83)		
Bilirubin >1.2 mg/dL[a]	58, 62, 81, 86, 140	5	486	166	0.43	0.84	2.7 (0.85-7.9)	89	.001	0.69 (0.35-1.1)	83	<.001
WBC <4 x 10^3/μL	62, 81, 86	3	268	115	0.25	0.90	2.5 (0.72-8.7)	41	.18	0.90 (0.83-0.98)	0	.80
AST>ULN[b]	56, 66, 103, 106, 108	5	605	184	0.78	0.62	2.1 (1.2-3.6)	91	<.001	0.38 (0.21-0.67)	67	.02
Hb< 13 g/dL	60, 62, 81	3	269	99	0.45	0.80	1.9 (1.3-2.7)	0	.58	0.80 (0.62-1.0)	48	.15
ALT>ULN[a]	56, 71, 103, 108, 122, 128	6	1296	184	0.88	0.23	1.1 (0.99-1.3)	48	.08	0.54 (0.17-0.91)	46	.10
ALT>2 x ULN	61	1	213	113	0.53	0.35	0.82 (0.65-1.0)			1.3 (0.96-1.9)		

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; blank cell, not applicable because the finding comes from only 1 or 2 studies; GGT, γ-glutamyl transpeptidase; Hb, hemoglobin; LR, likelihood ratio; PT/INR, prothrombin time/international normalized ratio; ULN, upper limit of normal; WBC, white blood cell.

[a]Bivariate random-effects summary measures.

[b]Univariate random-effects summary measures because data did not converge on a bivariate solution.

Diagnostic Accuracy of Bonacini score

Bonacini CDS	# of studies	Total# of patients	# Patients w/cirrhosis	Sensitivity	Specificity	Positive LR/ *P value*	Negative LR/ *P value*
>8	5	613	113	0.25	0.96	13 / 0.003	0.77/ 0.01
>7	6	906	170	0.39	0.96	9.4/0.06	0.65/0.018
>3	5	756	196	0.90	0.32	1.4/<0.001	0.30/0.66

Bonacini Cirrhosis Discriminant Score

Platelets (x1000/mm^3):

- >340 – zero points
- 280 to 339 – one point
- 220 to 279 – two points
- 160 to 219 – three points
- 100 to 159 – four points
- 40 to 99 – five points
- <40 – six points

ALT/AST ratio

- >1.7 – zero points
- 1.2 to 1.7 – one point
- 0.6 to 1.19 – two points
- <0.6 – three points

INR

- <1.1 – zero points
- 1.1 to 1.4 – one point
- >1.4 – two points

modified three parameter CDS by Dr. Maurizio Bonacini in 1997

Let’s Try Bonacini on This Case

- 52 year old international business owner seeking 5 million whole life.
- MVR reveals DUI in 2005
- Current labs: CBC with MCV 110, platelets 140,000

  LFTs: Total bili 1.5, AST 80, ALT 55

  Lipids: HDL 75, triglycerides 300

  A1C 6.2, glucose 145

  MVR 2/16 treated in ED, discharged, labs noted INR 1.5

Can any one explain why there is an INR in Labs done in emergency dept?

Calculations on our 52 yr old applicant

- Platelets 140K — 4 points
- ALT/AST = 55/80 = 0.68 — 2 points
- INR = 1.5 — 2 points

\+

\+

score 8 points

Caution: Bonacini scores are only relevant on those who are suspect for liver disease.

FibroTest or FibroSure

marketed in Europe **marketed in USA**

- Non invasive method developed by Australian investigators
- Validated Predictor of Liver Fibrosis using 3 ccs of fasting blood
- Score from 0-1
- Based on age, gender and these 6 serum analytes:

1) Serum bilirubin
2) ALT
3) GGT
4) Alpha 2 macroglobulin
5) Alpha 2 globulin (haptoglobin)
6) Apolipoprotein A1

- FibroTest has been recommended the first line assessment for fibrosis with untreated Chronic Hepatitis C in 2006 by the French National Authority for Health

FibroTest or FibroSure

The equation for calculating the FibroTest score regression coefficient (logistic regression) is:[6]

$$z = 4.467 \times \log_{10}[1.9(g/L)] - 1.357 \times \log_{10}[0.652(g/L)] + 1.017 \times \log_{10}[60(IU/L)] + 0.0281 \times [36)]$$

$$+1.737 \times \log_{10}[18.126(\mu mol/L)] - 1.184 \times [1.45(g/L)] + 0.301 \times 1 - 5.54$$

Score of $\leq$ 0.31 had NPV of 91%

Score > 0.48 had PPV for significant fibrosis of 61% and score > 0.72 had PPV of 76% for advanced fibrosis

Significant fibrosis corresponds to F2, F3, F4

Advanced Fibrosis corresponds to F3 and F4

Contraindication for use of FibroSure/FibroTest includes Gilbert's disease, acute hemolysis, extrahepatic cholestasis, post transplantation and renal insufficiency

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FibroTest/FibroSure Reference Interval

Fibrosis stage

- F0 (no fibrosis) 0.00 – 0.21
- F0-F1 : 0.22 – 0.27
- F1 (portal fibrosis) 0.28-0.31
- F1-F2 : 0.32-0.48
- F2 (bridging fibrosis w/ few septa) 0.49-0.58
- F3 (bridging fibrosis w/ many septa) 0.59-0.72
- F3-F4 : 0.73-0.74
- F4 (cirrhosis) 0.75-1.00

FibroTest	METAVIR
0.75-1.00	F4
0.73-0.74	F3-F4
0.59-0.72	F3
0.49-0.58	F2
0.32-0.48	F1-F2
0.28-0.31	F1
0.22-0.27	F0-F1
0.00-0.21	F0

VALID NO MATTER THE ETIOLOGY OF LIVER DZ

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HepaScore or FibroScore

= y/ y+1

Y= exp[-4.185818- (0.0249 x age) + (0.7464 x sex)

+ (1.0039 x alpha2-macroglobulin) = (0.0302 x hyaluronic acid)

+ (0.0691x bilirubin) – (0.012 x GGT)]

Score from 0-1 using these units:

Age = years

Sex (male = 1 and female =0)

Alpha2-macroglobulin (g/L)

Hyaluronic acid (microgram/L

Bilirubin (micromole/L)

GGT U/L

HepaScore or FibroScore

Score of ≤ 0.2 has NPV 98%, thus, excludes fibrosis (means F0)

Score ≥ 0.8 has PPV for predicting cirrhosis of 62%

Thus HepaScore is excellent method to rule out significant fibrosis

FibroScan

FibroScan

- Historical background: Palpating for liver firmness since 1500 BC and has been the usual practice since 1930
- FibroScan introduced in Europe in 2003
- Approved in April 2013 by the FDA in US
- Painless rapid test (15 minutes)
- Shear waves measure the elasticity of the liver using technique called Vibration controlled Transient Elastography (VCTE)
- Units are called kPa (kilopascals) – higher the number, greater the stage of fibrosis – score range 2.5-75 kPa
- **Caution: the degree of stiffness varies according to type of liver disease. For example, cut off for cirrhosis is lower in Hepatitis B and C and higher for ALD and cut off even lower in NAFLD**

Magnetic Resonance Elastography

- Applies a probe to back of patient that results in emission of low frequency vibrations through liver, which are then measured through MRI spin echo sequence
- Meta-analysis of 5 trials comparing MRE to liver bx show sensitivity of 94% and specificity of 95% in differentiating F0-1 from F2-4
- Sensitivity of 98% and specificity of 94% differentiating F0-3 from F4
- Meta-analysis of 12 retrospective studies concluded MRE has high accuracy for diagnosis of significant or advanced fibrosis and cirrhosis**, independent of BMI and etiology of CLD**
- Case series from Children's Hospital in Cincinnati: Lead author found MRE can accurately detect fibrosis in children including those whom are severely obese with NAFLD and other forms of chronic liver

Use of FibroScan in Clinical Practice

Key Points

- To determine severity of fibrosis prognostically and identifying who would most benefit from treatment
- For those receiving treatment, can determine response to treatment
- Useful in identification those who warrant variceal and HCC screening
- Higher cut off values correspond to higher fibrosis stages
- Cut off values differ among different liver diseases

46

FibroScan Use in Hepatitis C

Stiffness	Indicates	Advice
> 12.9 kPa	Cirrhosis NPV = 95%	US and AFP every 6 months for surveillance of Liver Cancer. Strongly consider HCV therapy
≥ 9.6 kPa	Advanced Fibrosis ≥ F2	Strongly consider HCV therapy
< 7.1 kPa	Lower level of fibrosis < F2 NPV> 90%	Consider HCV therapy vs. Observation

FibroScan Use in Hepatitis B

Stiffness	Indicates	Advice
> 12.9 kPa	Cirrhosis	US and AFP every 6 months for surveillance of Liver cancer. Strongly consider HBV therapy
≥ 7.3 kPa	≥ F2 PPV = 94%	Strongly consider HBV therapy
5.2-7.2 kPa	Lower level of fibrosis	Observation if low HBV viremia. Repeat FibroScan in 1 year
< 5.3 kPa	< F2 NPV=83%	Observation if low HBV viremia

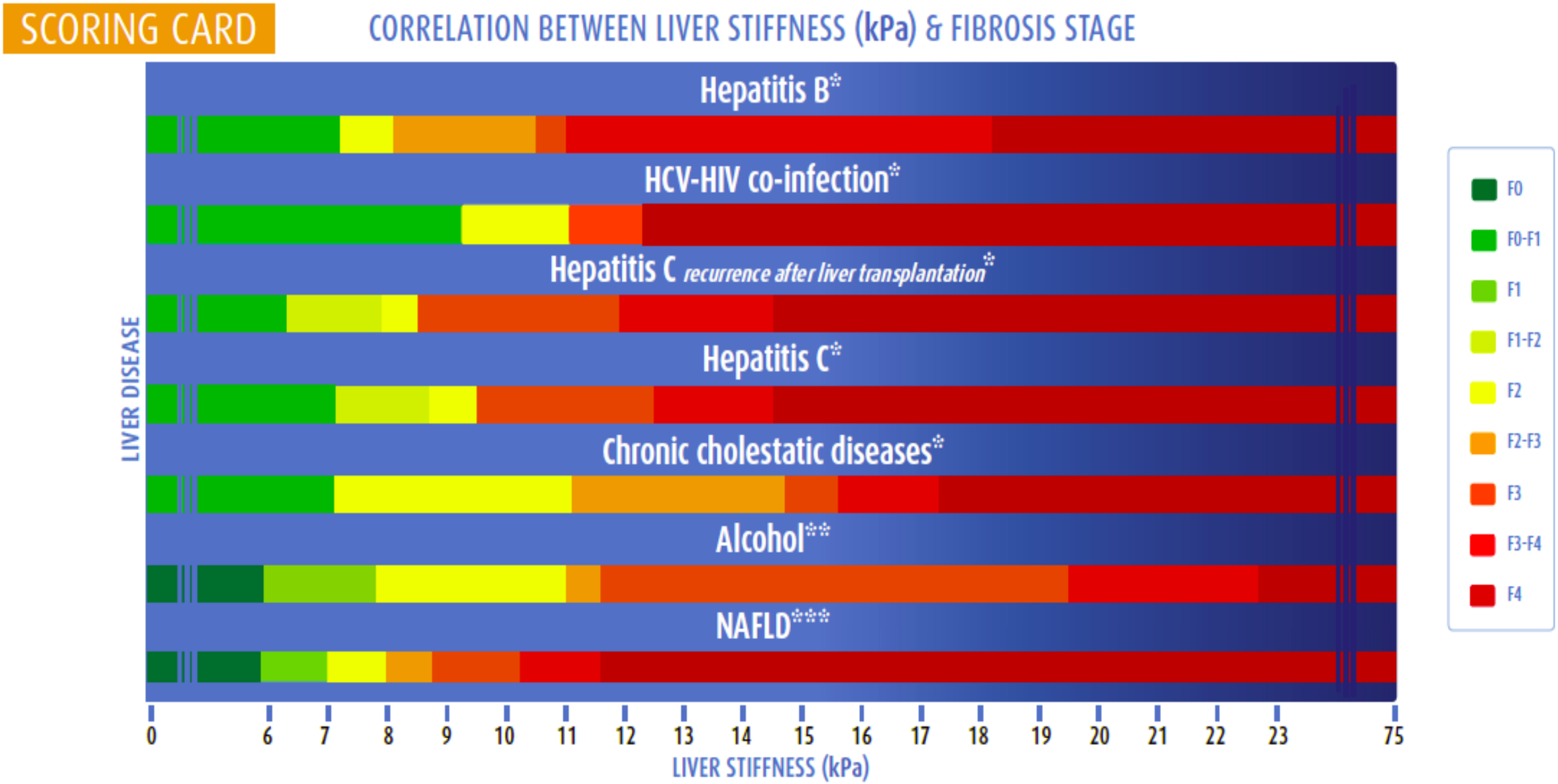
FibroScan Use in Non Alcoholic Fatty Liver (NAFLD)

Stiffness	Indicates	Advice
> 10.2 kPa	Cirrhosis PPV = 99%	Refer to Hepatology. US and AFP every 6 months for surveillance of liver cancer
≥ 7.9 kPa	≥ F3 PPV=97%	Refer to Hepatology, may need therapy (Vitamin E) or enter clinical trial
6 – 7.8 kPa	F2	May observe in Primary Care. Repeat FibroScan in 1 year
<6 kPa	Lower level of fibrosis	Observe in Primary Care. Diet and exercise. DM and HLD control

FibroScan Use in Alcoholic Liver Disease (ALD)

Stiffness	Indicates	Advice
> 18.7 kPa	Cirrhosis PPV = 90%	US and AFP every 6 months for surveillance of Liver cancer. Stop all alcohol
12.7-18.7 kPa	≥ F3 Advanced fibrosis PPV=92%	Stop all alcohol. Consider US and AFP every 12 months for surveillance of Liver cancer
> 8.2-12.6	≥ F2 Advanced fibrosis PPV = 100%	Stop all alcohol

Fibrosis Scoring Card



Pop Question

Which testing result is most compatible with cirrhosis in a patient with Chronic Active Hepatitis B?

A. kPa of 7.2

B. HepaScore result of 0.52

C. FibroSure result of 0.80

Pop Question

Which condition is most likely associated with Cirrhosis with a kPa of 10.5?

A. ALD
B. NAFLD
C. Hepatitis B
D. Hepatitis C

CASES

Case 1

45 year old IT specialist in US for last 10 yrs from Vietnam. Has hx of hepatitis B. Hx GERD and diet controlled DM. Recent evaluation by hepatologist.

Paramed: BP 145/85, Height 5'9" Wt 200 (91 kg)
Insurance labs: LFTs: AST (SGOT) 145 (3.6xULN), ALT (SGPT) 155 (3.5xULN), Albumin 3.2, Glucose 155, A1C 7.2. CDT neg
Hepatitis C Antibody neg; Hepatitis B Ag reactive

APS from GI/Hepatology:
8/16
Exam: mildly obese, palmar erythema, few facial spider nevi, abdominal exam notes questionable fluid wave, slightly distended with no hepatosplenomegaly.
Labs: Hepatitis Be Ag reactive. Hepatitis B viral load 18,131,576 IU/ML
CBC: Platelets 130K nml otherwise; AFP 2.1, INR 2.0

FibroTest ordered. Test on next slide. MD initiated Viread for diagnosis of chronic active Hep B

Liver Fibrosis, FibroTest™ ActiTest™ Panel

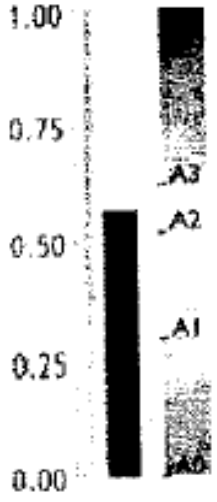
Fibro Test

Fibro Test assesses the fibrosis of the liver

Score : 0.77
(F4)
severe fibrosis

Acti Test

Acti Test assesses activity (inflammation in chronic viral hepatitis C or B)



Score : 0.57
(A2)
significant activity

Lab: QNI

Biomarkers

Analyte	Result	Reference Range/Comments
Alpha2 Macroglobulin	275	106-279 mg/dL
Haptoglobin	**236 H**	43-212 mg/dL
Apolipoprotein A1	**89 L**	94-176 mg/dL

Analyte	Result	Reference Range/Comments
Total Bilirubin	1.1	0.2-1.2 mg/dL
Gamma GT	**366 H**	3-95 U/L
ALT	65 H	9-46 U/L

Liver Fibrosis History

Previous Results
No historical results currently available.

What Concerns You?

- Chronic Active Hepatitis B from endemic region
- Physical exam findings
- Lab findings
- No liver bx however FibroTest score
- Try a Bonacini score
- What Risk Assessment?

Put a Bonacini on this case!!

Platelets 130K	4 points
ALT/AST 155/145 = 1.06	2 points
INR 2.0	2 points
	8 points

Case 2

36 yo male (6’0”/108 kg) with hx of Ankylosing Spondylitis HLA B27 positive. Presents with acute rise in chronically elevated LFTs

Baseline LFTs: AST 50, ALT 70 On Humira and Sulfasalazine

APS most recent Labs: AST 73, ALT 151, Total Protein 8.2, Albumin 4.8, Bili 1.2, INR 0.9

C Reactive Protein 30 (<3.0 mg/L)

CBC with Hgb/HCT 17/49

Alpha 1 Antitrypsin 289 (83-199)

Ceruloplasmin 62 (18-36 mg/dL)- Wilson’s ?

SMA(Smooth muscle Ab) negative – R/O AIH

ANA screen negative

Transglutamin IGA and Mitochrondrial AB not elevated – R/O PBC

A1C 5.0, Hep BS AG neg, HepC Ab neg

Ferritin 455 (12-410 ng/mL) Iron, TIBC , Iron Sat normal

SERUM HIV						
SERUM HIV	NON-REACTIVE			NON-REACTIVE		
BLOOD CHEMISTRY PROFILE						
GLUCOSE	96			60 -	109	(MG/DL)
BUN	18			9 -	25	(MG/DL)
CREATININE	0.8			0.7 -	1.5	(MG/DL)
ALK. PHOS.	85			30 -	125	(U/L)
BILI. TOT.	1.2			0.2 -	1.5	(MG/DL)
AST(SGOT)		53	H	0 -	33	(U/L)
ALT(SGPT)		109	H	0 -	45	(U/L)
GGT(GGTP)		131	H	0 -	65	(U/L)
TOT. PROTEIN	7.4			6.1 -	8.2	(G/DL)
ALBUMIN	4.9			3.8 -	5.2	(G/DL)
GLOBULIN	2.5			1.9 -	3.7	(G/DL)
CHOLESTEROL		230	H	140 -	199	(MG/DL)
HDL CHOLESTEROL	47			35 -	80	(MG/DL)
LDL (CALCULATED)	123			0 -	129	(MG/DL)
CHOL/HDL CHOL RATIO	4.9			<	5.0	
LDL/HDL RATIO	2.63			0.9 -	5.3	
TRIGLYCERIDES		298	H	0 -	150	(MG/DL)
HEPATITIS TEST						
HBsAg	NEGATIVE			NEGATIVE		
HEPATITIS C Ab	NEGATIVE			NEGATIVE		

GGT is 2 x ULN AST is 1.6 x ULN ALT is 2.4 x ULN

Recommendation by his rheumatologist:

Liver biopsy to make a diagnosis, possible autoimmune hepatitis vs NAFLD and FibroScan for staging. If drug injury suggested by Biopsy, will hold Humira. It will be difficult to distinguish between primary autoimmune hepatitis vs. Humira induced drug toxicity

Fibroscan

- Results: Patient had median Liver Stiffness Score of **6.1 kPa**, ranging from a low value of 5.4 to high of 8.8 kPa. The interquartile range to Median ratio was 13% The measure CAP controlled attenuation parameter rate was **348 dB/m**

- Fibrosis Interpretation: Metavir Fibrosis Stage 6.1 (2.5-7 kPa) (F0) No Significant Fibrosis

  (7-9.5 kPa) (F1-F2) Mild Fibrosis

  (9.5-12.5 kPa) (F3) Advanced Fibrosis

  (> 12.5 kPa) (F4) Severe Fibrosis/Cirrhosis

- Steatosis Stage: 201 +/- 44 (S0) No Steatosis

  253 +/- 44 (S1) Mild Steatosis

  321 +/- 42 (S2) Moderate Steatosis

  335 +/- 43 (S3) Severe Steatosis

UNINTERPRETABLE Note: Patient reported drinking 16 oz beer 2 d prior to test and ALT elevated > 100. both of these would usually falsely elevate elastography scores. Given his low score, the conclusion of his study is likely unchanged. Difficult to interpret if the severe steatosis suggested by CAP is accurate given these complicating factors. Per history, patient is scheduled for biopsy

US Abdomen report

- Normal liver size with smooth borders. Liver parenchyma is echogenic throughout. No focal hepatic lesions identified. Spleen is mildly enlarged up to 13.8 cm in maximal dimension. No ascites.
- Impression: Hepatic steatosis Mild splenomegaly

Liver Biopsy Pathology Report

Severe macrovesicular steatosis, **mild** lymphocytic steatohepatitis and increased hepatocellular nuclear glycogen. Consistent with NASH. Stage 0 or no fibrosis. No stainable iron, copper or A1AT globules.

What is the Ratable Condition?

What is the Ratable Condition?

- NASH of course!

Case 3

- Baby Boomer born USA 1957: Age 59 male with clean medical hx.

Agent asking for low substandard, maybe a T 2

- Insurance Labs: AST 33 (0-33), ALT 95 (0-45), GGT 30, CDT neg,

  HepBS Ag nonreactive, HepCAb reactive

- That is all you have. Does anyone see low substandard or STD?

Agent asking how to improve rating?

1) Non invasive liver testing

2) Treatment with Direct acting viral agents like Harvoni and then repeat noninvasive liver testing after Sustained Viral Response

Definition of Sustained Viral Response (SVR) is undetectable viral load at least 6 months after end of treatment … Considered a cure.

Recommendations on HCV RNA Follow-up After SVR

Organization	Recommendation
AASLD/IDSA	▪ Additional testing can be considered at ≥ 24 wks post treatment for pts with ALT increases to > ULN
EASL	▪ Noncirrhotics should be tested for ALT and HCV RNA at 48 wks post treatment and discharged if ALT normal and HCV RNA negative

- Note that HCV antibody tests will remain positive for most after cure and need not be repeated
- Reinfection can occur

AASLD/IDSA Guidelines. September 2017. EASL Guidelines. 2016.

Slide credit: clinicaloptions.com

Fibroscan Results Obtained

Fibroscan 8.5 kPa

Would the offer change?

Stiffness	Indicates	Advice
> 12.9 kPa	Cirrhosis NPV = 95%	US and AFP every 6 months for surveillance of Liver Cancer. Strongly consider HCV therapy
≥ 9.6 kPa	Advanced Fibrosis ≥ F2	Strongly consider HCV therapy
< 7.1 kPa	Lower level of fibrosis < F2 NPV> 90%	Consider HCV therapy vs. Observation

Applicant Gets on Harvoni with SVR

<u>6 months</u> after 12 weeks of Harvoni, non detected Hep C

Repeat Fibroscan 6.0 kPa

What would you rate him now??

Case 4

42 yo international businessman applying for 5 million whole life

PMH: **smoker**. Drinks socially. HTN on Lisinopril. HLD on Lipitor. GERD on Prilosec OTC. Last executive physical 1/17.

Paramed: 6'2" 205lbs BP 140/90 EKG normal

Insurance Labs: BUN 25, Creatinine 1.2, Glucose 95, A1C 5.5%, **GGT 77**(1.6 x nml) , **AST 85** (2.1 x nml), ALT 65 (1.2x nml), **CDT +**, HepCAb nonreactive. HBSAg nonreactive. Tchol 225, LDL 105, **HDL 77**

MVR **DU**I 2011
Executive PE labs from 8 months prior to app:

CBC - WBC 5.0, Hgb/HCT 12.5/38, MCV 110, platelets 225K
LFTs - AST 66, ALT 49, T bili 0.9
Lipids – HDL 82

His brother is an MD and prescribes the Lisinopril and Lipitor

How would you underwrite him?

Who thinks this guy could have alcoholic cirrhosis?

Do a quick Bonacini. Could the value be above 7 to suggest cirrhosis?

Platelets 225k

ALT/AST = 65/85 = 0.76

INR….. Don't have. Do we even need it though?

Platelets (x1000/mm^3):
- >340 – zero points
- 280 to 339 – one point
- 220 to 279 – two points
- 160 to 219 – three points
- 100 to 159 – four points
- 40 to 99 – five points
- <40 – six points

ALT/AST ratio
- >1.7 – zero points
- 1.2 to 1.7 – one point
- 0.6 to 1.19 – two points
- <0.6 – three points

INR
- <1.1 – zero points
- 1.1 to 1.4 – one point
- >1.4 – two points

Asks his MD brother to order Fibroscan, thinking he could get a better rating

Fibroscan Results 8.1 kPa

Any rate change

Stiffness	Indicates	Advice
> 18.7 kPa	Cirrhosis PPV = 90%	US and AFP every 6 months for surveillance of Liver cancer. Stop all alcohol
12.7-18.7 kPa	≥ F3 Advanced fibrosis PPV=92%	Stop all alcohol. Consider US and AFP every 12 months for surveillance of Liver cancer
> 8.2-12.6	≥ F2 Advanced fibrosis PPV = 100%	Stop all alcohol

What if Fibroscan report was 19.5 kPa?

QUESTIONS?

55 yo diabetic female

Let's take a trip through APS LABS

CURRENT INSURANCE LABS

CITY: N/S | POLICY AMT: $ 100,000 | SENT: 04/02/2019 21:59
STATE/ZIP: TX/78602 | AGENCY: D01 NYL AUSTIN | LAST FOOD: 12 HRS
DL#/ST: 12311346/TX | EXAMINER: APPS | URINE TEMP: IN RANGE
INSURANCE TYPE: LIFE

NSA: NOT SUITABLE FOR ANALYSIS
REPORT DELAYED DUE TO ADDITIONAL TESTS REQUESTED
SENT = REPORTED DATE
NSA: NOT SUITABLE FOR ANALYSIS-RESULT EXCEEDS HIGHER RANGE OF LINEARITY
ALL TESTS PERFORMED ON BLOOD UNLESS OTHERWISE SPECIFIED.

.	RESULT/STATUS		CUTOFF/EXPECTED VALUE
CHEMISTRIES----------			
GLUCOSE	99		70-110 mg/dL
HEMOGLOBIN A1C	7.4	HIGH	3.0-6.0 %
BLOOD UREA NITROGEN (BUN)	13		6-25 mg/dL
CREATININE	0.70		0.60-1.50 mg/dL
GFR (MAYO)	98.18		68.00-117.00 mL/min
ALKALINE PHOSPHATASE	100		30-115 U/L
TOTAL BILIRUBIN	0.45		0.10-1.20 mg/dL
SGOT (AST)	49	HIGH	0-41 U/L
SGPT (ALT)	23		0-45 U/L
GAMMA GLUTAMYLTRANSFERASE	88	HIGH	2-65 U/L
TOTAL PROTEIN	7.4		6.0-8.5 g/dL
ALBUMIN	4.2		3.9-5.5 g/dL
GLOBULIN	3.2		1.0-4.6 g/dL
CARDIAC RISK----------			
CHOLESTEROL	205		120-260 mg/dL
HIGH DENSITY LIPOPROTEIN(HDL)	58.1		25.0-75.0 mg/dL
TRIGLYCERIDES	169		10-200 mg/dL
CHOLESTEROL/HDL RATIO	3.52		1.50-5.00
SEROLOGY----------			
NT-PROBNP	15		0-124 pg/mL

Progress Notes by Bunch, Tina C, MD at 3/4/2014 3:55 PM (continued)

• SGPT (ALT)	02/18/2014	15	15 - 78 U/L	I
• SGOT (AST)	02/18/2014	22	9 - 44 U/L	I
• ALKALINE PHOSPHATASE	02/18/2014	147*	40 - 136 U/L	I
• PROTEIN, TOTAL	02/18/2014	8.4	6.7 - 8.8 g/dl	I
• ALBUMIN	02/18/2014	3.4	3.1 - 4.5 g/dl	I
• CALCULATED GLOBULIN	02/18/2014	5.0	3.1 - 5.0 g/dl	I
• CALCULATED A/G RATIO	02/18/2014	0.7	0.7 - 1.4 ratio	I
• Anion Gap	02/18/2014	5	5 - 15 mmol/L	I
• B/C ratio	02/18/2014	12.7	10.0 - 20.0 ratio	I
• WBC	02/18/2014	9.4	4.5 - 11.0 K/ul	I
• RBC	02/18/2014	4.44	3.80 - 5.10 M/ul	I
• HGB	02/18/2014	13.7	11.5 - 15.5 g/dl	I
• HCT	02/18/2014	40.2	34.0 - 45.0 %	I
• MCV	02/18/2014	90.5	80.0 - 100.0 fL	I
• MCH	02/18/2014	30.8	27.0 - 34.0 pg	I
• MCHC	02/18/2014	34.1	31.0 - 36.0 g/dl	I
• PLT	02/18/2014	248	150 - 400 K/ul	I
• RDW				

14181308 — — 09/10/16 0

Component	Value	Reference Range	Flag
Sodium	139	135 - 145 mm/L	—
Potassium	4.1	3 5 - 5 1 mm/L	—
Chloride	105	96 - 109 MM/L	—
ECO2	30	23 - 33 mm/L	—
Glucose Random	303	70 - 100 mg/dl	H
Nonfasting Range 70-130 mg/dl			
BUN	13	7 - 22 mg/dl	—
Creatinine Serum	0 79	0 50 - 1 40 mg/dl	—
eGFR Non-African Amer	>60	>60 00 mL/min/1.73m^2	—
eGFR African Amer	>60	>60 00 mL/min/1.73m^2	—
Ca	9 3	8 4 - 10 2 mg/dl	—
Bilirubin Total	0 7	0 0 - 1 2 mg/dl	—
SGPT (ALT)	78	15 - 78 U/L	—
SGOT (AST)	90	9 - 44 U/L	H
Alkaline Phosphatase	170	37 - 127 U/L	H
Protein Total	7.8	6.7 - 8.8 g/dl	—
Albumin	3 7	3 1 - 4 5 g/dl	—
Globulin Total	4 1	2 8 - 4 4 g/dl	—

77

ID	Type	Source	Collected
14554184	—	—	07/07/17 0

Components

Component	Value	Reference Range	Flag
WBC Count	4.4	4.0 - 10.0 K/ul	—
RBC	4.61	3.80 - 5.10 M/ul	—
HGB	14.3	11.5 - 15.5 g/dl	—
HCT	41.7	34.0 - 45.0 %	—
MCV	90.5	80.0 - 100.0 fL	—
MCH	31.0	27.0 - 34.0 pg	—
MCHC	34.3	31.0 - 36.0 g/dl	—
PLT	162	150 - 400 K/ul	—
RDW	[illegible]	[illegible]	

REGION VI OFFICE CLINIC

MRN [illegible], DOB
Visit date 11/9/2017

		2	
Ca	9 4	8 4 - 10 2 mg/dl	—
Bilirubin Total	0.8	0.0 - 1.2 mg/dl	—
SGPT (ALT)	74	15 - 78 U/L	—
SGOT (AST)	155	9 - 44 U/L	H
Alkaline Phosphatase	159	37 - 127 U/L	H
Protein Total	8 9	6 7 - 8 8 g/dl	H
Albumin	4 0	3 1 - 4 5 g/dl	—
Globulin Total	4 9	2 8 - 4 7 g/dl	H
A/G Ratio	0 8	0 7 - 1 4 ratio	—
Anion Gap	6	5 - 15 mmol/L	—
B/C Ratio	15 0	10 0 - 20 0 ratio	—

78