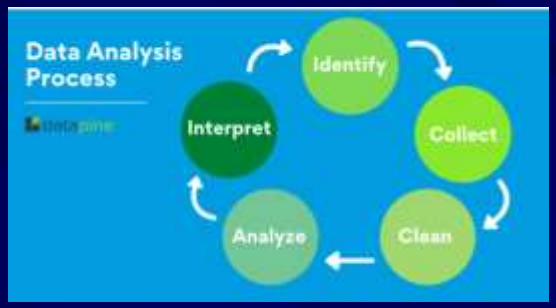


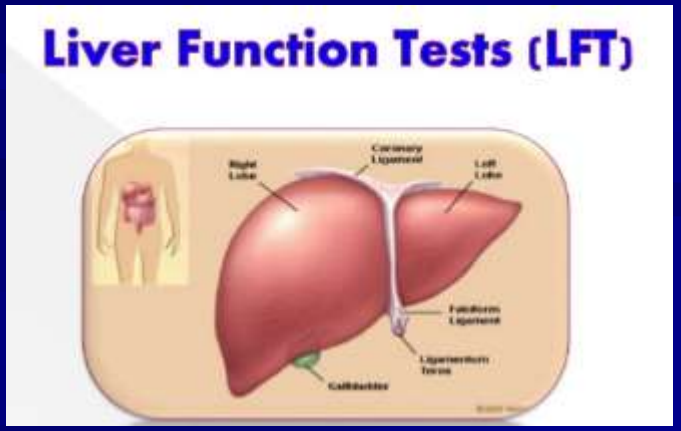
Clerk/NP/FNP必修課程

Clinical application of Laboratory data (2025)

臨床檢驗數據-案例為中心.

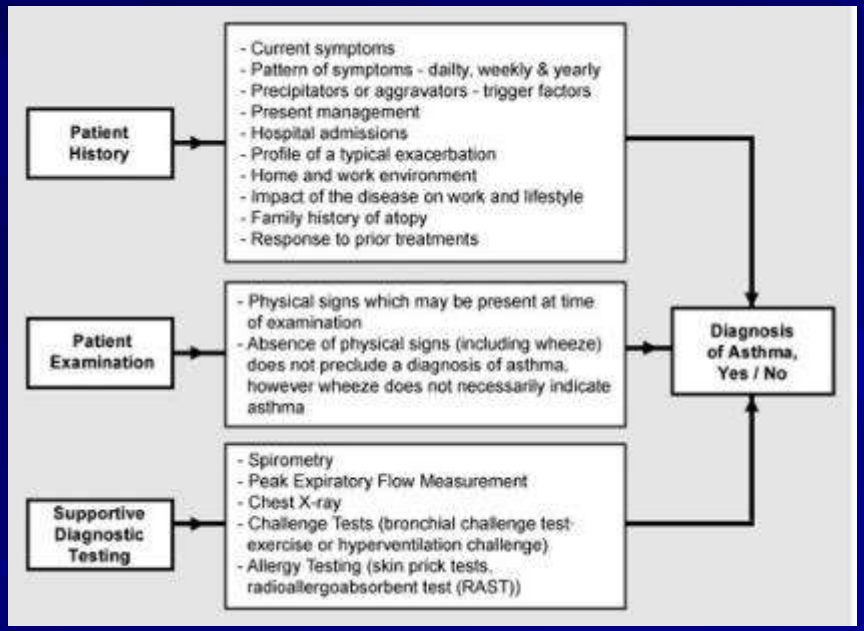
Cheng-Yi WANG

2025.04.18



臨床診斷中重要的藉助

診斷步驟:三從,四得



- 好好問病史,會得到新的資訊.
- 好好檢查身体,(PE)會得到疾病的變化--->診斷的証據
- 好好注意檢驗數據、會得到診斷的線索-→診斷的証據
- 綜合以上各個異常,會得到整体的印象以確定診斷.

Laboratory tests

Laboratory tests之價值

- Diagnostic—直接指出疾病
- AC sugar : 200, HbA1c: 7.7-→DM
- Severity ---看出嚴重性,
- CRP>12, Bilirubin > 5 mg/dl, HB :<8 gm/dl
- 某一些疾病/狀態之可能性
- CEA>5,→ Cancer or false positive
- MCV<80-→ microcytic change-→**Fe. Deficiency or**
- **chronic blood loss**
- 特殊應用
- BUN/ Cr. >30 indicated bleeding in UGI tract

BUN to Cr. ratio

The plasma BUN/creatinine ratio is usually 10 to 15:1 (when both are expressed as mg/dl)

- BUN: exogenous + endogenous,
- Cr: endogenous
- **BUN/Cr : normally 10-20**

BUN:Cr	Urea:Cr	Location	Mechanism
>20:1	>100:1	Prerenal (before the kidney)	BUN reabsorption is increased. BUN is disproportionately elevated relative to creatinine in serum. Dehydration or hypoperfusion is suspected.
10-20:1	40-100:1	Normal or Postrenal (after the kidney)	Normal range. Can also be postrenal disease. BUN reabsorption is within normal limits.
<10:1	<40:1	Intrarenal (within kidney)	Renal damage causes reduced reabsorption of BUN, therefore lowering the BUN:Cr ratio.

- Upper Gi bleeding was suspected when BUN/Cr.> 30
- Lower Gi bleeding When BUN/Cr remained 10-20

CY Wang et al (1973),
First APCDE in Kyoto

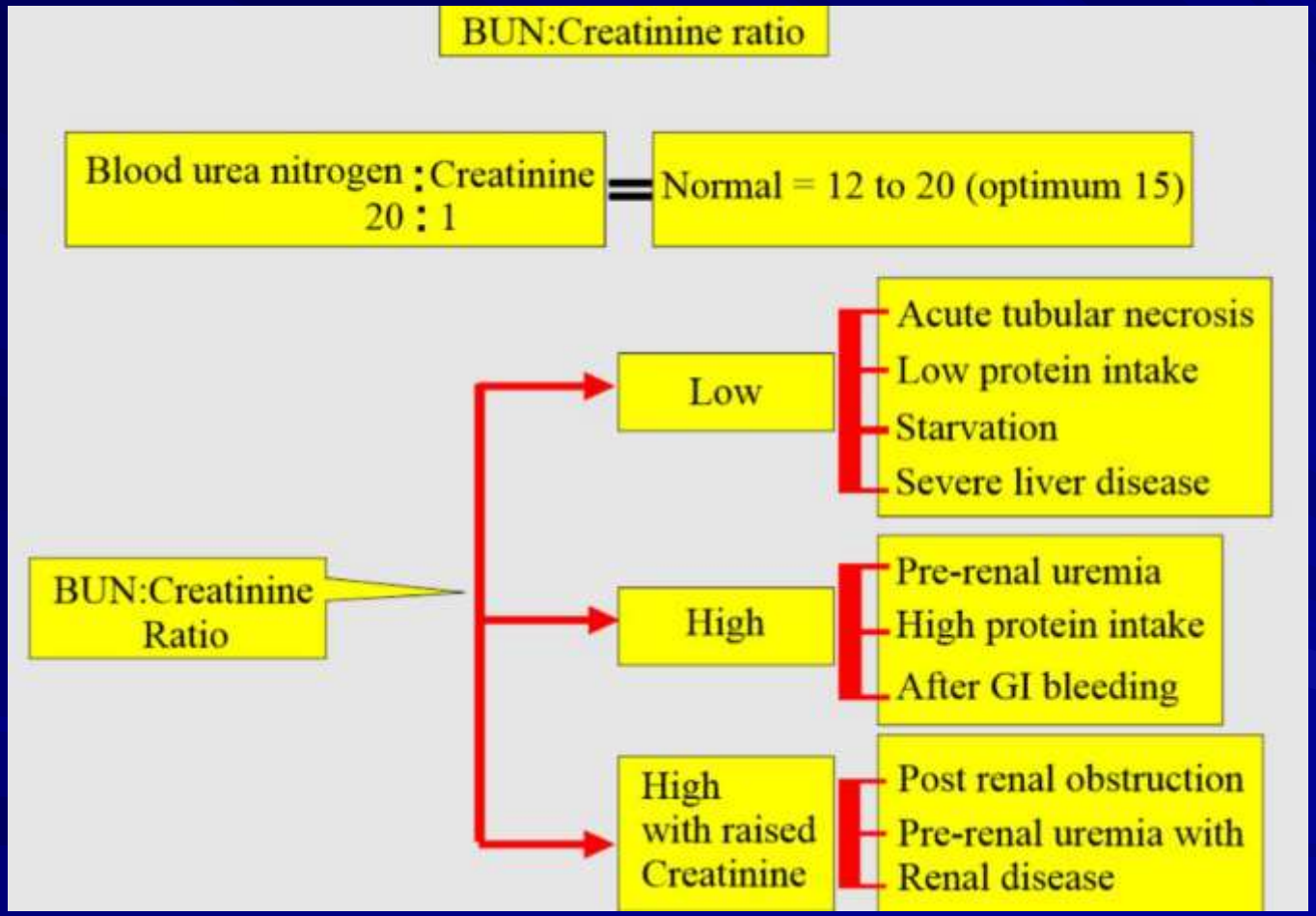
- Diagnostic—直接指出疾病
- AC sugar : 200, HbA1c: 7.7-→DM
- AFP>10,000→肝癌
- Amylase 500+ or Lipase 100-→ acute pancreatitis

- Severity ---看出嚴重性,
- CRP>12,
- Bilirubin > 5 mg/dl,
- HB :<8 gm/dl, severe
- Anemia.

Low serum Ca—in pancreatitis

Acute necrotizing pancreatitis, severe.

Bun/Cr, ratio: normal 12 ~ 20



Ratio 低:是因為 Cr. 高

Ratio高, 是因為 BUN高,好像吃高蛋白植物后引起. 上消化道出血流出的血在小腸吸收, ratio 就會高 (Cr. 可能正常)

Gastrointestinal bleeding

- The ratio is useful for the diagnosis of bleeding from the gastrointestinal (GI) tract in patients who do not present with overt vomiting of blood. **In children, a BUN:Cr ratio of 30 or greater has a sensitivity of 68.8% and a specificity of 98%** for upper gastrointestinal bleeding.

- A common assumption is that the ratio is elevated because of amino acid digestion, since blood (excluding water) consists largely of the protein hemoglobin and is broken down by digestive enzymes of the upper GI tract into amino acids, which are then reabsorbed in the GI tract and broken down into urea. However, elevated BUN:Cr ratios are not observed when other high protein loads (e.g., steak) are consumed. *Renal hypoperfusion secondary to the blood lost from the GI bleed has been postulated to explain the elevated BUN:Cr ratio*. However, other research has found that renal hypoperfusion cannot fully explain the elevation.

- Ref. Urashima M, Toyoda S, Nakano T, et al. (July 1992). "BUN/Cr ratio as an index of gastrointestinal bleeding mass in children". *J. Pediatr. Gastroenterol. Nutr*. **15** (1): 89–92

Overt UGI bleeding

- Manifest symptoms for three hours or more.
- Not fresh blood vomiting only.
- Tarry stool passage (+)

- **BUN:Cr ratio of 30 or greater indicated bleeding from the upper g-I tract.**
- **Check urgent UGI endoscopy :**

Lesions (+)

Evidence of bleeding (+)

檢驗的思考羅輯

- 1.事前思考:我為何作這個檢驗:**目的**在診斷還是排除一個疾病.
- 2.**期待值**是什麼:
- 正常值,還是不正常?
- 3. **結果**是什麼?
- 期待值或非期待值-→
- 4. 那代表何種意義.
- **診斷確立**,嚴重度知,
- 還是**意料之外**,另有問題

每一個檢驗數據都要思考
1.我為什麼要做這個檢驗
2.結果是不是與我想像的一致.
3.如果意料之外,如何解釋.

Biochemical data
-and pancreatitis

- *** Amylase, lipase, and CRP in different periods of pancreatitis同階段不同的數據,不正常或正常

I. Amylase : 1240 (24 hours after onset)----pancreatitis
Amylase :120 (84 hours after onset)-----not diagnostic

- II. Lipase : 680, CRP: 0.3 (24 hours after onset): CRP: normal
- Lipase : 310 (84 hours after onset)------→diagnostic for pancreatitis
- III. CRP: 0.6 (28 hours after onset)---data was still normal,
- CRP : 3.8 (84 hours after onset) ----indicated active pancreatitis
- CRP: 18.6 (126 hours after onset : pancreatitis still active -→necrotizing pancreatitis
- amylase : 80, lipase :178 (126 hours after onset) : reduced, still not normal-→一定要知道time off onset

Lab. Data 配合病情去解釋-1

- 1. Time of onset of disease---檢驗是哪一
- 天的. 有什麼樣的結果.
- @疾病開始的6個小時內很多變化還沒出現
- (no data abnormality)
- @ 某些數據3天以後才出現變化 (CRP)
- 有些數據3天以後已經正常(amylase)
- @大部分數據在疾病活動其中一直都是
- 不正常. (CEA,CRP, WBC)
- @某些數據在疾病過程中可能有些波動 (AFP)
- @ 小心不同的檢驗方法會有不同的結果(CEA)(HBsAg)

Lab. Data 配合病情去解釋-2

- 2. 治療開始後(也包括病情自然減輕)Lab data 會存相關的變化
- (1) 改善 (improved, subsided, remitted)
- (2) 近乎完全治癒 nearly healed, healed
- (3) 尚未改變—可能還要一段時間才改善,
- 也可能是無效 (no change, “stable” disease)
- (4) 惡化—很可能是治療無效(ineffective)
- **@@ 必須注意是治療開始幾天后所做的檢查.**
- **@.沒有改善是warning signs,要思考對策.**
- **@@@不同疾病治療反應時間並不相同**

Response time after therapy,
initial response

- 1. 一般的疾病, 包括 bacterial infection,
- 3天可見分曉.
- 2. Fungal infection– one week
- 3. TB : 7-10 days.
- 4. Cancer : about 1-2 months,
- 5. rare diseases : 可能要7天,
- 快速反應改善-→表示治療選擇是正確的
- 注意老人與小孩可能有不同的反應
- 注意疾病也同時在進行中 **Progression of disease.**

注意一些治療之后可能產生的變化-新的疾病的發生

- 1. Post-transplantation.—cancer, infection, -- CV diseases, etc.
  - 器官移植是延長許多終末期器官衰竭患者生命的唯一途徑。該程式自啟動以來並非沒有涉及相關風險。**癌症是器官移植后死亡的三大原因之一**。心血管疾病和感染是器官移植后死亡的另外兩個原因，但由於有效的篩查、預防和介入治療，它們的頻率都在下降。關於早期發現和缺乏既定指南，對移植后惡性腫瘤的瞭解不足。由於免疫動力學改變、宿主反應和不同的臨床表現，風險因素最難以捉摸。研究表明，器官移植后患癌症的風險總體上增加了 2 到 4 倍。腫瘤發生涉及的機制是長期免疫抑制導致對腫瘤細胞的免疫監視減少，以及移植后的機會性感染，尤其是由於 EB 病毒 （EBV）、水痘、巨細胞病毒 （CMV） 和人皰疹病毒 （HHV）-8 等引起的病毒感染。醫生和患者都面臨著一個具有挑戰性的問題，即器官移植后的癌症更具生物侵襲性，並且由於合併症和對移植排斥反應的恐懼，患者可能會接受不太侵襲性的癌症治療

Posttransplantation Cancer

Shekhar Gogna [1], Karan Ramakrishna [2], Savio John [3]

In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan. 2023 Sep 4.

注意一些治療之后可能產生的變化—你又再發了

- 2. Relapse of diseases
- @True relapse
- @ Relapse because of previous life
- habits—diet, alcohol---故態復萌
- @ Not true relapse but occurrence of
- diseases.—new disease.

New diseases ” transplanted” from the donor

- 1.Screening of **donor** and candidate prior to solid organ **transplantation**-Guidelines from the American Society of **Transplantation** Infectious **Diseases** Community of Practice.Malinis M, Boucher HW; AST Infectious Diseases Community of Practice.
- 2019.
- 美國移植學會（American Society of Transplantation） 傳染病實踐區（Infectious Diseases Community of Practice of the American Society of Transplantation） 指南的這一更新部分回顧了實體器官移植前供體和候選者的篩查。供體和候選者的篩選對於優化移植后結局至關重要。基於詳細病史和適當診斷性評估的風險評估至關重要。**某些病毒感染的血清學篩查很重要，有助於免疫諮詢和降低受者的風險。除血清學檢查外，已故和活體供體還需要進行乙型肝炎、丙型肝炎和人類免疫缺陷病毒的核酸檢測。某些地方性暴露可能需要在推薦的標準檢測之外進行額外評估。如果供體或受體被診斷為感染，則需要治療以及額外的檢測和/或預防，以降低移植后併發症的風險。移植前即刻的某些感染可能需要延遲移植。**

精神層面層面的影響

- 2. The experiences of living with a **transplanted** kidney from a deceased **donor**.Petre OA, Crăciun IC, Băban A.J Ren Care. 2021 Mar;47(1):58-67. doi: 10.1111/jorc.12349. Epub 2020 Sep 23.PMID: 32964692
- BACKGROUND: Kidney **transplantation** is considered an optimal treatment option for patients with end-stage kidney **disease** in terms of survival rate, quality of life and cost-effectiveness. ...

移植後的病人在長程生活中出現的問題有新的疾病
Real world data.
從已故捐獻者那裡獲得腎臟的經歷對接受者來說是一個複雜的心理挑戰。這項研究是獨一無二的，因為它展示了移植經歷的精神層面，以及接受者對移植和器官捐獻的看法如何受到他們的宗教和文化背景的影響，表明瞭整體護理方法的重要性。

疾病再發有眾多的因素，如何預先估計危險性

Bone marrow Transplant 2025 Mar;60(3):310-318.
doi: 10.1038/s41409-024-02480-3. Epub 2024 Nov 25.

A multifactorial risk scoring system for the prediction of early relapse in CMML patients with allo-HSCT: a nationwide representative multicenter study

Jian-Ying Zhou[#1], Yu-Xiu Chen[#1], Hai-Long Yuan[2], et al

慢性粒單核細胞白血病（CMML）是一種Clonal 造血幹細胞惡性腫瘤，唯一可治癒的療法是同種異體造血幹細胞移植（allo-HSCT）。然而，allo-HSCT 並不適合所有 CMML 患者，復發是治療失敗的主要原因。進行一項全國性的多中心真實世界研究，以開發一種新的早期復發預測評分系統。在國際血液和骨髓移植登記中心（CIBMTR）資料庫的公開研究數據集中，共有來自 27 個醫療中心接受同種異體 HSCT 治療的 238 名 CMML 患者，以及 307 名接受同種異體 HSCT 治療的成年 CMML 患者。根據競爭風險回歸方法**確定移植后 CMML 早期復發的獨立預後因素。確定了 4 個預後因素**：

骨髓原始細胞 >10%（風險比 [HR]，4.262;），年齡 > 60 歲（HR，6.221;）、血紅蛋白水準 <100 g/L（HR， 3.695;）和非 TET2 基因突變（HR，3.425;）。基於回歸係數開發風險分級評分系統，將患者分為低風險（0-1 分）、中風險（1.5-2 分）和高危（> 2 分）組。經驗證的內部 c 統計量為 0.767，外部 c 統計量為 0.769 。在衍生佇列中，低風險、中風險和高風險組早期復發的累積發生率分別為 1.35% (1-4%)、10.40% (4-16%）和 29.54% (16-39%）。該評分系統可用於早期識別復發風險高的患者，並有助於實施緊急醫療支援。

TET2: Tet methylcytosine dioxygenase 2

- **四甲基胞嘧啶雙加氧酶 2（*TET2*）**是一種人類基因。[5]它位於4q 24 染色體上，該區域在患有各種髓系惡性腫瘤的患者中表現出復發性微缺失和拷貝中性雜合性丟失

IgA nephropathy seminar nephron: 2024-2025

2025.151570.

- **Post-transplant IgA Nephropathy**
- Song C Ong [1], Bruce A Julian [2]

免疫球蛋白 A（IgA） 腎病是許多國家最常見的腎小球腎炎。大多數患者進展為腎衰竭，腎移植是最佳治療方法。不幸的是，IgA 腎病通常在移植后復發並縮短同種異體移植物的存活率。免疫抑制可改變移植后 IgA 腎病的臨床表達。生物標誌物已在天然腎 IgA 腎病中被鑒定和研究，但需要在移植中得到驗證。復發性 IgA 腎病的治療取決於支援措施，這些措施主要來自自體腎 IgA 腎病的證據

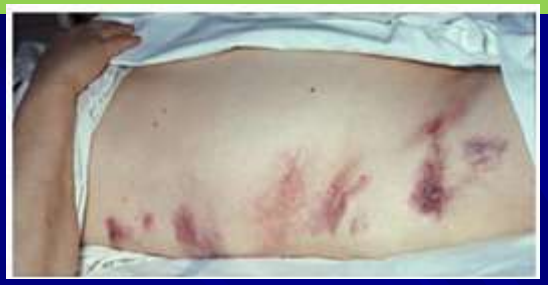
任何疾病都要確認診斷依據

- @ history—symptoms,
- @ PE—signs
- @ Laboratory—data
- @ Images: target organ /distant
- metastases—common images,

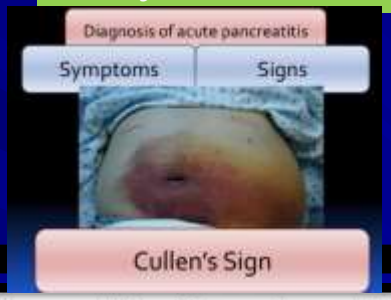
參考學會發表的guidelines
Textbook.
Clinical experience.
每一個VS 在回診時需要告知（VS Round）

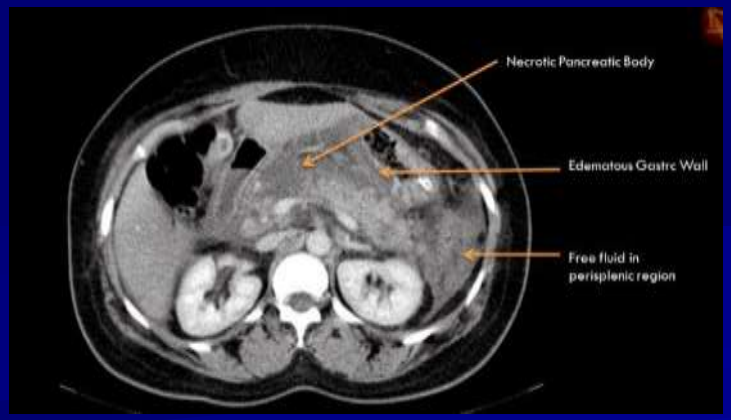
急性胰臟炎之診斷:.診斷依據

- 1, 診斷急性胰臟炎必需符合以下三個條件之二:
  - (1) 典型的上腹痛—向前灣屈較輕,躺平加重、會痛到背後
  - (2) **Serum amylase** 及 **lipase** 明顯升高, 即正常值之**3**倍以上.
    - **Amylase > 500 .**
    - **Lipase :>200**
  - (3) **Images : US, CT, MR**可見胰臟腫大,出水或有壞死或一般**X**光上出現片段性小腸腫大**(sentinel loop).**



Grey Turner's sign





Acute Pancreatitis - Diagnosis and Classification

- Diagnosis (two of three features)
  - Abdominal pain
  - Serum lipase or amylase ≥ 3 times upper limit of normal
  - Characteristic findings on imaging study (CT, MRI or ultrasound)
- Revised Atlanta Classification of Acute Pancreatitis (2012)*
  - **Categories**: interstitial edematous and necrotizing
  - **Mild**: no organ failure, no local or systemic complications, and generally resolves within 1 week
  - **Moderate**: transient organ failure, local complications, or exacerbation of co-morbid disease
  - **Severe**: persistent organ failure (>48 hours)
    - Mortality higher (~ 30%) in patients with severe AP
    - Severe disease accounts for ~15-25% of presentations

Severity predicted from Clinical data

- 如何判斷疾病的嚴重性.
- (1)symptoms/signs沒有好轉
- (2)Lab data 沒有改善
- (3) Images 出現更多更嚴重的變化
- extent of disease, severity of disease.
- Complications.

Acute severe pancreatitis
predicted from lab. data

- **Role of Clinical, Biochemical, and Imaging Parameters in predicting the Severity of Acute Pancreatitis.**
- Zerem D[1],et al (Bosnia) : Euroasian J Hepatogastroenterol. 2017 Jan-Jun;7(1):1-5.
- 84 patients (65.6%) had mild and 44 (34.4%) had severe AP. The severity markers were significantly different between the mild and the severe groups ($p < 0.001$). **Leukocyte count, serum albumin level, C-reactive protein (CRP), Ranson, acute physiology and chronic health evaluation II (APACHE II), and Glasgow score** were the factors associated with radiological **severity** grade. Leukocyte count, CRP, Ranson score, APACHE II, and Glasgow score were the factors associated with the number and appearance of acute fluid collections (AFCs). A significant association was found between the number of AFCs and the occurrence of **complications** [odds ratio 4.4; 95% confidence interval 2.5-7.6]. was significantly longer in the group with severe disease as compared with the group with mild disease ($p < 0.001$).
- **Leukocyte count, serum albumin level,**
- **C-reactive protein (CRP),**
- **Ranson, acute physiology and chronic health evaluation II (APACHE II), and Glasgow score 很多data都要Follow up.**

單獨靠data也不可靠

- Reduction of data---better
- Serum data and urine data
- Ascites data – tumor markers, CEA, AFP etc.

Rupture of pancreatic duct
1.Trauma
2.Tumor
3.Acute pancreatitis
4.----

- 胰管內管狀乳頭狀腫瘤伴隨遠端主胰管破裂一例報告
- Intraductal tubulopapillary neoplasms with rupture of the distal main pancreatic duct: a case report
- 清水雄二蘆田亮 杉浦貞一et al *外科病例報告* **Vol** 210（2020)
- Case presentation: A 73-year-old woman presented to a local hospital with epigastric discomfort and pain. Abdominal multidetector-row computed tomography (MDCT) revealed a 2.5-cm hypovascular tumor in the pancreatic body with distal pancreatic duct dilatation and a slightly low-density area spreading over the ventral side of the pancreatic body. Endoscopic ultrasonography and fine-needle biopsy of the tumor revealed adenocarcinoma of the pancreas. She was referred to our hospital 2 months later. MDCT performed at our hospital showed no significant change in the tumor size or pancreatic duct dilatation. However, the low-density area at the ventral side of the pancreas had shrunk; therefore, this finding was considered to have been an inflammatory change. Under a preoperative diagnosis of resectable pancreatic ductal adenocarcinoma, distal pancreatectomy was performed. The final diagnosis was ITPN with associated invasive carcinoma. Macroscopically and microscopically, the main pancreatic duct (MPD) had ruptured at the distal side of the tumor, and the fistula connected the MPD and extrapancreatic scar tissue. Conclusions: ITPN with rupture of the pancreatic duct is extremely rare. In the present case, a sudden increase in the pancreatic duct internal pressure or acute inflammation likely caused the rupture of the MPD.

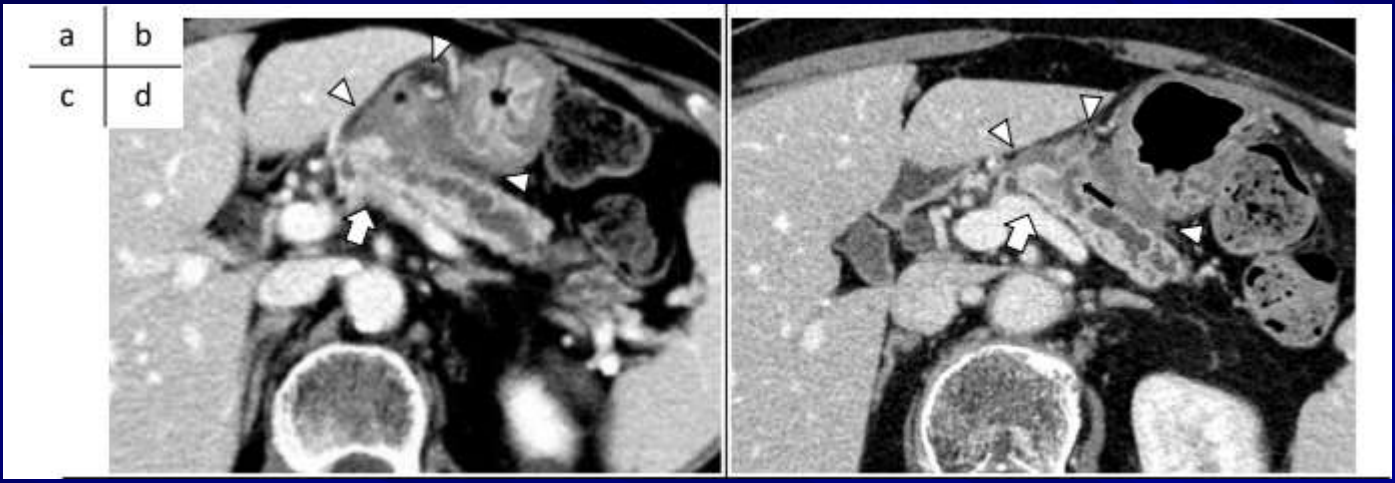


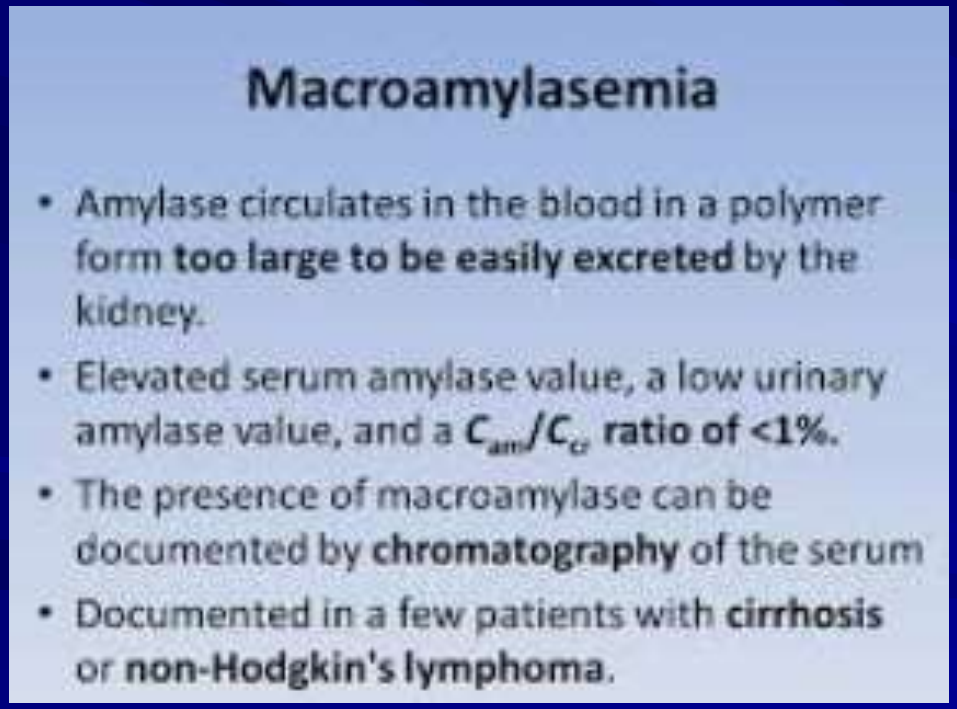
Fig. 1 Imaging findings. a Abdominal multidetector-row computed tomography (MDCT) at the referral hospital. A hypovascular tumor was present in the body of the pancreas (arrow), and the distal pancreatic duct was dilated. In addition, a slightly low-density area (LDA) was found to be spread over the ventral side of the pancreas (arrowhead) and touching the stomach. b MDCT images obtained 2 months later at our hospital. There was no significant change in the tumor size (arrow) or pancreatic duct dilatation, but the LDA at the ventral side of the pancreas had shrunk (arrowhead). The two-tone duct sign and cork-of-wine-bottle sign were observed (arrow). Retrospective examination revealed findings that seemed to indicate the rupture of the main pancreatic duct (MPD) and the formation of a fistula extending outside of the pancreas (black arrow)

Lipase D1很高、D2下降一半以上表示severe

- **Predicting severe acute pancreatitis in children based on serum lipase and calcium: A multicentre retrospective cohort study.** Bierma MJ[1], et al(Australia) : Pancreatology. 2016 Jul-Aug;16(4):529-34.
- 175 AP episodes (including 50 severe episodes [29%]) were identified. Serum lipase ≥50% decrease on D2 (sensitivity 73%, specificity 54%) **and calcium trough ≤2.15 mmol/L (8.6)**within 48 h (sensitivity 59%, specificity 81%) were identified as statistically significant predictors for severe AP. By combining the newly identified predictors with the previously validated predictor serum lipase ≥7× ULN on D1 (sensitivity 82%, specificity 53%), specificity improved to predict severe AP on D2 with the addition of: (i) serum lipase ≥50% decrease (sensitivity 67%, specificity 79%), or (ii) trough calcium ≤2.15 mmol/L (sensitivity 46%, specificity 89%).
- **Severe :lipase D2/D1 < 50 % + Ca : < 8.6 mg/dl**

Macroamylasemia

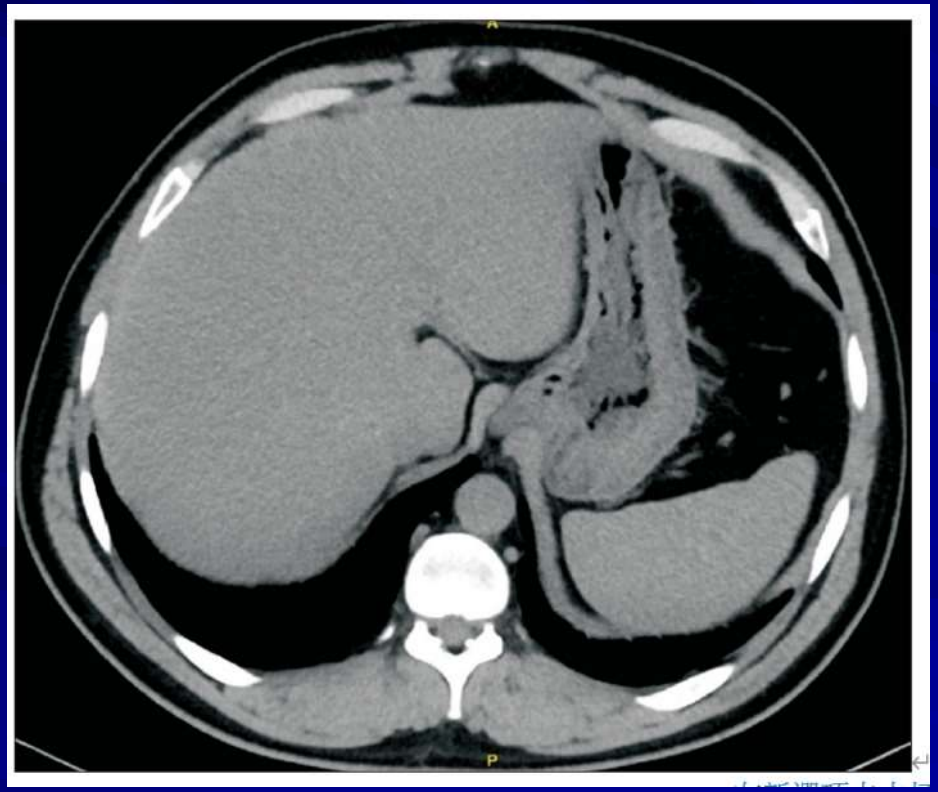
- 血液中之amylase 很高,但urine 裡面的 amylase 正常就要思考 macroamylasemia.



患者為 35 歲女性，其血清澱粉酶活性（約 234 U/L）持續高於參考上限，而其他實驗室檢查結果包括脂肪酶、AST、ALT、GGT、肌酸酐和尿素均正常。尿澱粉酶水平下降（290 U/L）。 2014年住院期間發現澱粉酶升高。患者表現為慢性餐後消化不良，無其他臨床症狀。該患者不飲酒、不吸煙，除母親患有慢性胰臟炎外，無其他相關疾病或家族病史。腹部超音波檢查、胃鏡檢查和磁振造影胰膽管攝影 (MRCP) 沒有發現病灶。內視鏡超音波檢查和大腸鏡檢查結果正常，因此排除了胰臟疾病。乳糜瀉、寄生蟲疾病、食物過敏檢查結果也均為陰性。也排除了藥物的影響，糞便彈性蛋白酶檢查呈現陰性。根據以上結果，懷疑患有大澱粉酶血症。

Another case

- 2019 年 11 月進行的腹部電腦斷層掃描顯示胰腺和肝膽系統正常（圖1）
- 2021年1月進行的食管胃十二指腸鏡檢查和結腸鏡檢查結果正常



胰腺無病理變化。

- 使用以下公式分析血清和尿澱粉酶和肌酐以計算澱粉酶肌酐清除率（ACCR）：
- **[尿澱粉酶（U/L）x血清肌酐（mg/dL）]**
- **_____ x 100 (%)**
- **[血清澱粉酶（U/L）x尿肌酐（mg/dL）]。**
- 正常的 ACCR 為 3%-5%，
- **而 <1% 的結果提示巨澱粉酶血症** 。
- 檢測結果如下：尿澱粉酶，238 U/L;血清肌酐，0.71 mg/dL;血清澱粉酶，370 U/L;尿肌酐，293.42 mg/dL。ACCR 計算為 0.155%;因此，確定了巨澱粉酶血症的診斷
- **尿澱粉酶，238 U/L**
- **血清澱粉酶，370 U/L**

血清肌酐，0.71 mg/dL
尿肌酐，293.42 mg/dL

澱粉酶肌酐清除率（ACCR）(0.155%)

巨澱粉酶血症Macroamylasemia是一種罕見的良性疾病

- 巨澱粉酶血症是一種罕見的良性疾病，其特徵是血清澱粉酶水準升高，但尿澱粉酶水準正常，
- 沒有其他相關體征和癥狀。
- 大澱粉酶是一種大分子複合物，由免疫球蛋白結合的澱粉酶組成，免疫球蛋白的大尺寸會阻止腎臟濾過。
- 它通常引起高澱粉酶血症，ACCR 為 <1%。
- 巨澱粉酶血症在一般人群中的患病率約為 1%，在高澱粉酶血症患者中約為 2.5% 。它主要存在於男性中;然而，也有一些病例見於兒童和新生兒 [7]。

•. 2000 Dec;39(12):1115-8.

Simultaneous macroamylasemia and macrolipasemia

- **Simultaneous macroamylasemia and macrolipasemia in a patient with systemic lupus erythematosus in remission** H Goto [1] et al : (Akita University School of Medicine.) Internal Med. 2000 Dec;39(12):1115-8.

A 39-year-old woman had been treated for systemic lupus erythematosus from 1982 to 1993. She was found to have an unexplained increase in serum amylase and lipase activities since 1996. Immunoprecipitation assay showed that amylase was bound to IgA2-kappa and IgA1-kappa (IgA2 > IgA1), whereas lipase was bound to IgA1-kappa. During a follow-up period up to December 1999, the patient did not develop any additional autoimmune or lymphoproliferative disorders.

Routine blood analysis in 1996 and 1997 showed that amylase and lipase activities were increased [602 IU// (normal range: 56-176) and 736 IU/ / (9^-0), respectively]. Amylase and lipase activities were measured on Hitachi 7350 and 7170 automated analyzers with test kits from Daiichi

2. Tumor markers
cancer screening, staging and evaluation of response

- Tumor markers :

  AFP and CEA : 判斷primary or metastatic liver cancer.

  AFP, abnormal, >200----→HCC

  CEA, > 20 -----→Metastatic cancer,

Cancer screening

- Positive rate :quite low (50 %)
- False positive rate : quite high.
- Specificity : acceptable.

Expected to have new markers, new methods.

Cancer staging

- Effective
- CEA-- > 20 might be advanced
- Ca199 > 10, 000 : diagnostic
- AFP: > 10,000 : diagnostic

Often needs staging workup by imaging

Therapeutic response

- Effective ,if it was abnormal before treatment.

Primary or secondary liver cancers

- 1. History of chronic liver disease, which was associated with HCV or HBV,
- 2. Chronic history of HBsAg carrier
- 3. **AFP was more than 400**.單一腫瘤/多個腫瘤
- ----------
- 4. History of primary cancer at other organ.
- 5.Primary cancer was not treated radically within 2-3 years.
- 6. **CEA was abnormal and high** (more than 20)
- 7. Multiple tumors scattered in both lobes.

TABLE 2 The expression levels of four markers in different groups

Groups	n	PIVKA-II (mAU/mL)	AFP (ng/mL)	AFP-L3 (ng/mL)	CEA (ng/mL)
Normal control	116	21.9 (19.58-24.97)	2.71 (2.14-3.77)	3.44 (2.33-5.09)	1.56 (1.02-1.90)
CLD	89	23.4 (16.01-39.17)	4.7 (2.81-7.29)[a]	3.21 (2.0-5.41)	2.14 (1.3-3.14)[a]
PHC	120	2000 (43.44-29771.36) [a,b]	149.39 (8.01-2000)[a,b]	11.02 (6.83-12.25)[a,b]	2.90 (1.93-4.29)[a,b]
MHC	115	40.19 (27.56-138.34)[a,b,c]	4.27 (2.56-10.57)[a,c]	4.32 (3.22-5.33)[a,c]	10.04 (2.98-782.40)[a,b,c]
H		192.26	152.93	159.59	174.61
P		.000	.000	.000	.000

[a]vs normal control group.
[b]vs chronic liver disease group.
[c]vs PHC group, $P \leq .05$.

primary HCC (PHC), metastatic HCC (MHC), chronic liver disease (CLD),

J Clin Lab Anal. 2020 May;34(5):e23158. doi: 10.1002/jcla.23158. Epub 2019 Dec 10.

The diagnostic value of PIVKA-II, AFP, AFP-L3, CEA, and their combinations in primary and metastatic hepatocellular carcinoma

Famei Qi [1], Aihua Zhou [1], Li Yan et al (China)(
Department of Clinical Laboratory, Gansu Provincial Hospital, Lanzhou, China.

(L1905-1906)

PIVKA-II (DCP)

- PIVKA-II is also known as des gamma carboxy prothrombin (DCP) and is an abnormal prothrombin molecule that is generated due to acquired defect in the posttranslational carboxylation of the prothrombin precursor in malignant cells. In 1984, Liebman et al used a radioimmunoassay to detect serum PIVKA-II levels in patients with HCC and found that 91% of patients showed a significant increase. This finding has since been successfully applied in clinical practice.11 PIVKA-II combined with Golgi protein 73 (GP73) showed higher accuracy than AFP in early HCC diagnosis.12 PIVKA-II.

Liebman HA, Furie BC, Tong MJ, et al. Des-gamma-carboxy (abnormal) prothrombin as a serum marker of primary hepatocellular carcinoma. N Engl J Med. 1984;310(22):1427-1431.

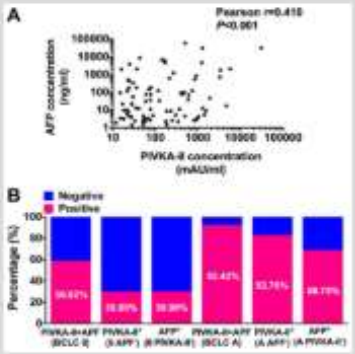


Figure 2.

Overlap between PIVKA-II and AFP was low in early HCC. (A) Correlation between PIVKA-II and AFP levels in early HCC. Although there was a significant correlation between these biomarkers, the value of the Pearson correlation coefficient was low. (B) Positive rates of PIVKA-II and AFP detection in different subgroups with early HCC. PIVKA-II, prothrombin induced by vitamin K absence-II; AFP, α-fetoprotein; HCC, hepatocellular carcinoma

The rates of positive detection using the combination of PIVKA-II and AFP levels were 58.82 and 92.42% for stages 0 and A, respectively (Fig. 2B). In the stage 0 group, the PIVKA-II-positive rate of AFP-negative patients was 30.00%, the AFP-positive rate of PIVKA-II-negative patients was 30.00% (Fig. 2B). For the stage A group, the PIVKA-II-positive rate of AFP-negative patients was 82.76%, the AFP-positive rate of PIVKA-II-negative patients was 68.75%. Together, these results reveal low overlap between PIVKA-II and AFP levels in patients with early HCC and indicate the promise of combining PIVKA-II and AFP levels for managing these patients.

Significance of PIVKA-II levels for predicting microvascular invasion and tumor cell proliferation in Chinese patients with hepatitis B virus-associated hepatocellular carcinoma

•Authors: Xiao-Lu Ma et al. Oncology Letters. June-2018 Volume 15 Issue 6

Indexes	Normal control (n = 116)	CLD (n = 89)	PHC (n = 120)	MHC (n = 115)	χ^2	*P*
PIVKA-II	2 (1.7)	21 (23.6)	92 (76.7)	60 (52.5)	154.856	.000
AFP	0 (0.0)	20 (22.5)	89 (74.2)	37 (32.2)	177.3	.000
AFP-L3	0 (0.0)	18 (20.2)	89 (74.2)	15 (13.0)	135.250	.000
CEA	0 (0.0)	10 (11.2)	19 (15.8)	80 (69.6)	138.629	.000
PIVKA-II or AFP	2 (1.7)	21 (46.1)	110 (91.7)	76 (66.1)	115.921	.000
PIVKA-II or AFP-L3	2 (1.7)	39 (43.8)	111 (92.5)	70 (60.9)	113.386	.000
AFP or AFP-L3	0 (0.0)	38 (42.7)	110 (91.7)	49 (42.6)	116.702	.000

L1905-1906)

Lab data related to paraneoplastic syndrome

- 1. Serum Calcium--hypercalcemia
- 2. Blood glucose--hypoglycemia
- 3. Others

Hypocalcemia---acute necrotizing pancreatitis
Hypoglycemia related to hepatoma and other big tumor
Hypoglycemia related to insulin-like substance secretion.

Hypercholesterolemia in HCC

Hypocalcemia---acute necrotizing pancreatitis

- Hypocalcemia—**serum Ca : <8.8 mg/dl**
- Hypocalcaemia, also spelled hypocalcemia, is low calcium levels in the blood serum. The normal range is 2.1–2.6 mmol/L (**8.8–10.7** mg/dl, 4.3–5.2 mEq/L) with levels less than 2.1 mmol/l defined as hypocalcemia. Mildly low levels that develop slowly often have no symptoms. Otherwise symptoms may include numbness ...
- Ex. *Acute pancreatitis, --severe and with necrotizing changes, usually noticed at the 2nd-3rd day of disease.*
- **Hypercalcemia—serum ca : >10.7 mg/dl**
- Ex. Most cases are due to primary hyperparathyroidism or cancer.[1] Other causes include sarcoidosis, tuberculosis, Paget disease, multiple endocrine neoplasia (MEN), vitamin D toxicity, familial hypocalciuric hypercalcaemia, and certain medications such as lithium and hydrochlorothiazide.[1][2][3] Diagnosis should generally include either a corrected calcium or ionized calcium level and be confirmed after a week.[1] Specific changes, such as a shortened QT interval and prolonged PR interval, may be seen on an electrocardiogram (ECG).[

hypocalcemia

成人體內總鈣量約1000~1300g，99%以骨鹽形式存在於骨骼和牙齒中，其餘存在於各種軟組織中，細胞外液鈣僅佔總鈣量的0.1%，約1g左右。成人血鈣水平約為2.2~2.6mmol/L(8.8~10.4mg/dl)，主要以三種形式存在：①遊離鈣（50%），也稱離子鈣；②蛋白結合鈣（40%）；③可擴散結合鈣（10%）。

當血清白蛋白濃度在正常範圍時，血鈣低於2.2mmol/Ll(8.8mg/l) 正常值2.2~2.70 mmol/L，時稱為低鈣血症。不同醫院血鈣化驗參考值有小的差異，也有血鈣低於

: Blood :serum Ca < 2.1 mmol/L

Trousseau's sign (hand/finger spasms)

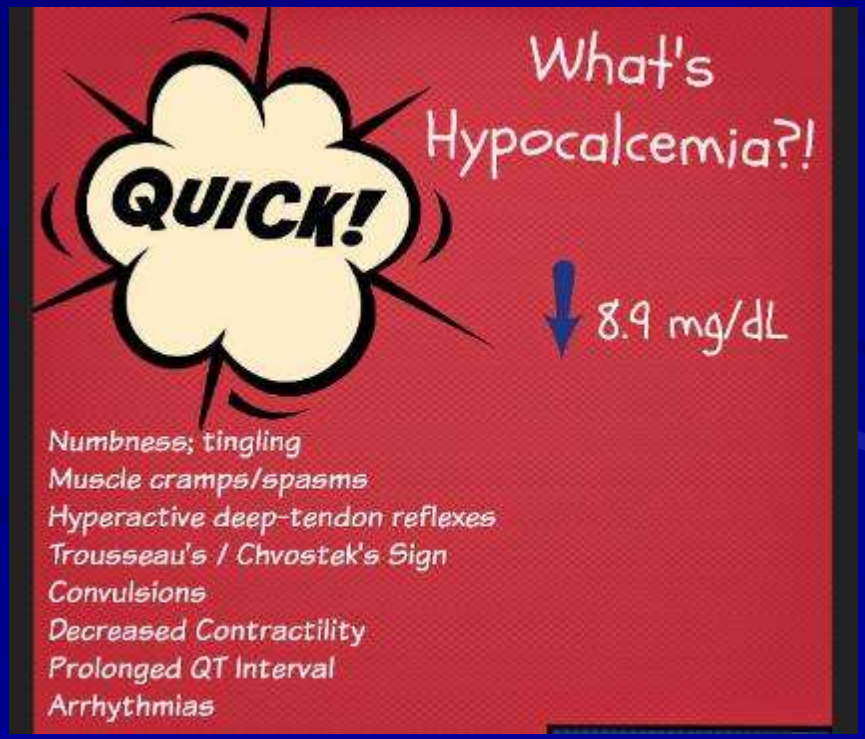
Watch for arrhythmias
(Prolonged QT interval, cardiac arrest…)

Increase in bowel sounds, diarrhea

Tetany

Chvostek's sign (facial twitching)

Hypotension, Hyperactive DTR



Hypocalcemic tetany

EXAMINATION TIP

Recognizing carpopedal spasm

In the hand, carpopedal spasm involves adduction of the thumb over the palm, followed by flexion of the metacarpophalangeal joints, extension of the interphalangeal joints (fingers together), adduction of the hyperextended fingers, and flexion of the wrist and elbow joints. Similar effects occur in the joints of the feet.

Trousseau's sign

Uncomfortable and very painful.

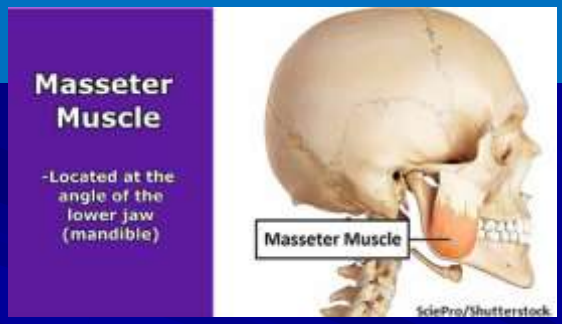
- A blood pressure cuff is inflated to 20mm Hg above systolic blood pressure level.
- arterial blood flow to the hand is occluded for 3 to 5 minutes.
- Carpopedal spasm:
  * flexion at the wrist
  * flexion at the MCP joints
  * extension of the IP joints
  * adduction thumbs/fingers

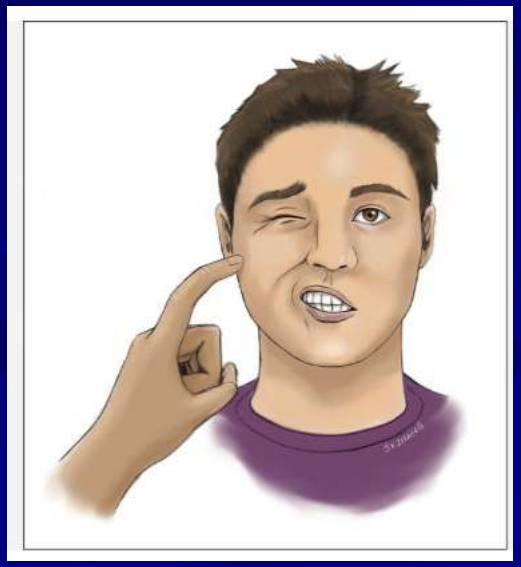
Chvostek sign

- The **Chvostek sign** (also **Weiss sign**) is one of the signs of tetany seen in hypocalcemia.
- It refers to an abnormal reaction to the stimulation of the facial nerve.
- When the facial nerve is tapped at the angle of the jaw (i.e. masseter muscle), the facial muscles on the same side of the face will contract momentarily due hyperexcitability of nerves.

Chvostek sign

- The Chvostek sign—a contraction of ipsilateral facial muscles subsequent to percussion over the facial nerve—is considered a clinical indicator of hypocalcemia.





Hypercalcemia related to cancer

Can Fam Physician. 2010 Mar; 56(3): 244–246.

PMCID: PMC2837688

PMID: 20228307

Cancer-related hypercalcemia

Dori Seccareccia, MD CCFP(EM) MClSc

Palliative care physician in the Department of Psychosocial Oncology & Palliative Care at Toronto General Hospital in Toronto, Ont.

Hypercalcemia affects up to 10% to 30% of cancer patients, and cancer-related hypercalcemia is the leading cause of hypercalcemia in hospitalized patients.[1,2] Patients with breast cancer, lung cancer, and myeloma are most commonly affected, but hypercalcemia can also occur with other malignancies, including renal, gynecologic, and head and neck cancers.[3,4] Unfortunately, cancer-related hypercalcemia has a poor prognosis, as it is most often associated with disseminated disease. Eighty percent of patients will die within a year, and there is a median survival of 3 to 4 months.

Hepatoma 也會出現 hypercalcemia

Hypercalcemia Secondary to a Primary Hepatoma

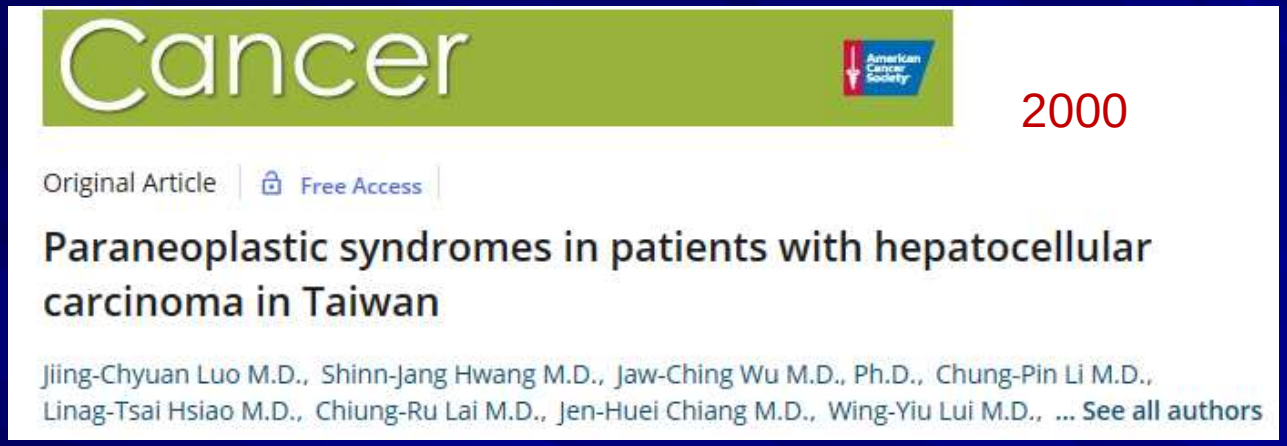
Reed T. Keller, MD; Irving Goldschneider, MD; Frederic W. Lafferty, MD

JAMA. 1965;192(9):782-784. doi:10.1001/jama.1965.03080220046020

1965

Paraneoplastic syndrome

Hepatoma associated with hypercalcemia



Cancer

2000

Original Article | Free Access

Paraneoplastic syndromes in patients with hepatocellular carcinoma in Taiwan

Jiing-Chyuan Luo M.D., Shinn-Jang Hwang M.D., Jaw-Ching Wu M.D., Ph.D., Chung-Pin Li M.D., Linag-Tsai Hsiao M.D., Chiung-Ru Lai M.D., Jen-Huei Chiang M.D., Wing-Yiu Lui M.D., ... See all authors

19.4 % in patients with hepatoma

A total of 232 of 1197 patients (19.4%) had paraneoplastic syndromes. HCC patients with paraneoplastic syndromes had significantly higher serum AFP; higher rates of initial main portal vein thrombosis, metastasis, and bilobal tumor involvement; larger tumor volume; and shorter survival than those without these syndromes. Patients with HBV-related HCC had a significantly higher prevalence of paraneoplastic syndromes than patients with HCV-related HCC (20.1% vs. 11.2%, $P = 0.005$). In a stepwise multivariate logistic regression analysis, AFP >50,000 ng/mL and tumor volume >30% were significant predictive variables associated with the presence of paraneoplastic syndromes in HCC patients.

Paraneoplastic syndrome in HCC

- A total of 232 of 1197 patients (19.4%) had paraneoplastic syndromes during the clinical course of HCC, of whom 177 had a single paraneoplastic manifestation, and 55 had multiple paraneoplastic manifestations.

- Single manifestation: 177/232 (76%)
- Multiple manifestations.

  55/232 (24 %).

Hypercholesterolemia-12.1 %

Hypoglycemia ----------5.3 %

Hypercalcemia ----------4.1 %

Erythrocytosis ----------3.1 %

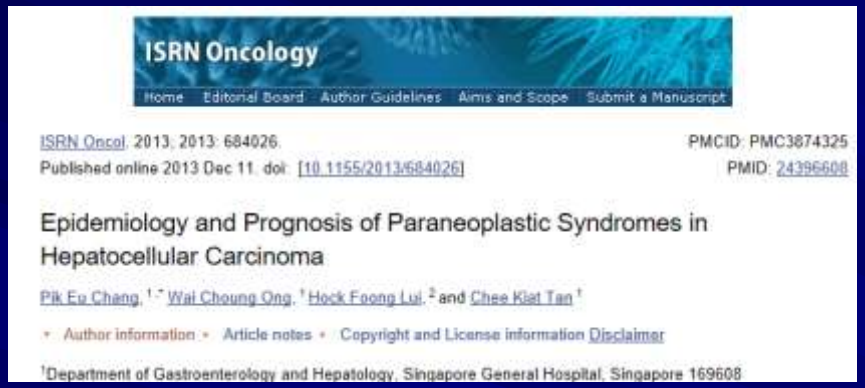
Characteristic	HCC patients with paraneoplastic syndromes (n = 232)	HCC patients without paraneoplastic syndromes (n = 965)	*P* value
Age (yrs)	61 ± 14	63 ± 11	0.042
Gender (male:female)	211:21	833:132	0.074
HBV:HCV related	154:21	609:166	0.006
Mean Child–Pugh score	6.8 ± 2.1	6.8 ± 2.2	0.894
Mean initial α-fetoprotein (ng/mL)	122,084 ± 280,188	23,719 ± 106,116	<0.001
Median (range)	2895 (3–1,621,700)	196 (3–1,892,500)	
Mean peak α-fetoprotein (ng/mL)	171,803 ± 352,790	35,695 ± 167,960	<0.001
Median (range)	8701 (3–2,055,300)	459 (3–2,975,570)	
Initial MPV tumor thrombosis (+:−)	60:172	125:840	<0.001
Initial metastasis (+:−)	61:171	112:853	<0.001
Tumor volume (%)	47.0 ± 25.1	20.1 ± 16.2	<0.001
Bilobal tumor involvement (+:−)	120:112	353:612	<0.001
Therapy for HCC (+:−)	100:132	523:442	0.003
Tumor cell arrangement (trabecular:mixed:acinar)	36:11:3	131:42:17	0.792
Tumor cell differentiation (Grade 1:2:3:4)	12:33:7:2	30:121:46:7	0.331
Median survival (days)	152	634	<0.001

Difference between HCC patients with or without paraneoplastic syndromes

Table 2. Comparison of Clinical and Laboratory Data and Tumor Features between Hepatitis B Virus- and Hepatitis C Virus-Related Hepatocellular Carcinoma Patients with Paraneoplastic Syndromes

Characteristic	HBV-related HCC with paraneoplastic syndromes (n = 154)	HCV-related HCC with paraneoplastic syndromes (n = 21)	*P* value
Age (yrs)	58 ± 14	67 ± 9	<0.001
Gender (male:female)	137:17	19:2	1.000
Mean Child–Pugh score	7.8 ± 2.4	7.2 ± 2.2	0.316
Mean α-fetoprotein (ng/mL)	182,218 ± 350,400	24,146 ± 54,989	<0.001
Median (range)	3598 (3–1,621,700)	597 (4–165,330)	
MPV tumor thrombosis (+:−)	54:100	4:17	0.224
Metastasis (+:−)	39:115	6:15	0.958
Tumor volume (%)	49.3 ± 23.7	42.5 ± 29.4	0.367
Bilobal tumor involvement (+:−)	79:75	9:12	0.469
Therapy for HCC (+:−)	40:114	9:12	0.175
Tumor cell arrangement (trabecular:mixed:acinar)	26:9:2	5:1:0	0.749
Tumor cell differentiation (Grade 1:2:3:4)	8:25:5:2	1:4:1:0	0.937
Median survival (days)	153	152	0.480

Difference between HBV-related and HCV related hepatomas



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PMCID: PMC3874325
PMID: 24396608

Epidemiology and Prognosis of Paraneoplastic Syndromes in Hepatocellular Carcinoma

Pik Eu Chang,[1,*] Wai Choong Ong,[1] Hock Foong Lui,[2] and Chee Kiat Tan[1]

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The prevalence, clinical characteristics, and survival of PNS among 457 consecutive HCC patients seen in our department over a 10-year period and compared them with HCC patients without PNS.

- *Results.*
- 1. PNS were present in 127 patients (27.8%).
- 2,The prevalence of paraneoplastic syndromes hypercholesterolemia,:24.5% hypercalcemia, 5.3 % erythrocytosis 3.9%,

3. Patients with PNS had significantly higher alpha-fetoprotein levels, more advanced TNM stage, and shorter survival.

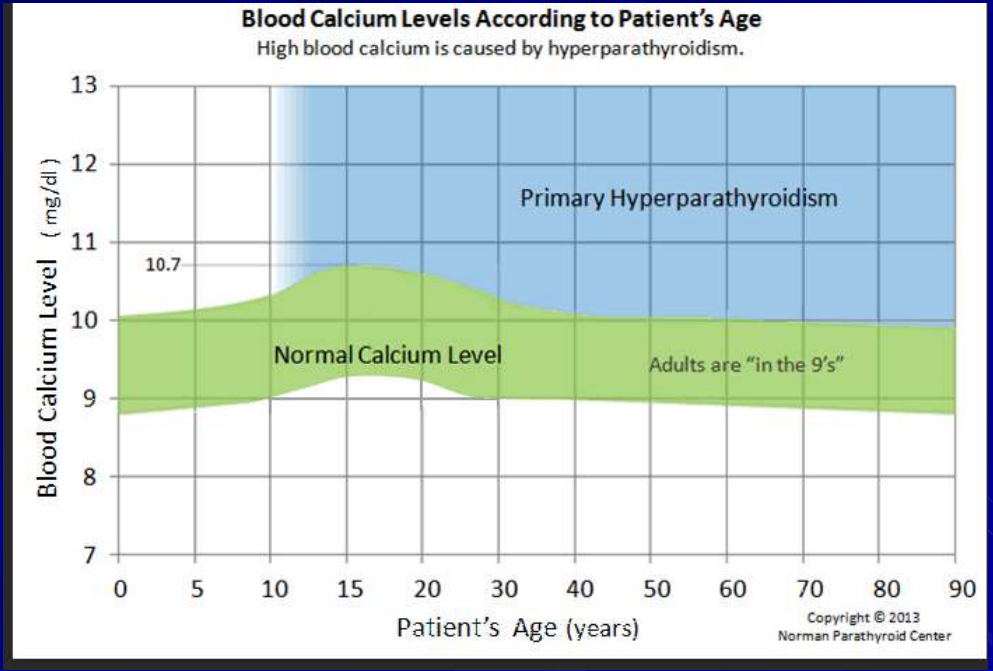
Corrected calcium
for albumin level (below 3,5 gm/dl)

Correct calcium for albumin level

- Normal serum level: 8.5–10.2 mg/dL
- 40% transported on albumin
- If hypoalbuminemia, use corrected calcium

Corrected calcium (mg/dL) =

serum calcium (mg/d) + 0.8(4.0 – serum albumin g/dL)



– corrected [Ca] in mmol/L =

= measured total [Ca] (mmol/L) + 0.02 x (40 – serum albumin in g/L)

Lab. Data 之來由:系列檢驗

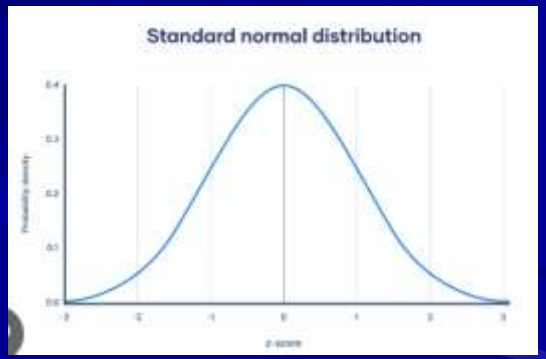
- 病人抽血→ 運送至 lab.
- 血液處理
- **檢驗**、人/機器

- Reading results → printed out → Hospital information networks醫院電腦索統
- →read and **interpreted** by clinicians
- 作對,但**讀错了還是滿盤全輸**

最嚴重的是 MISS INTERPRETED

從數據之讀取到分析→處理

- 從數據之讀取到分析---(臨床意義)--→**處理**
  Planning and action-→再評估其結果
- Normal----改善(由不正常變正常)
- Exclude a disease or diseases
- 排除某一種病
- Abnormal(High or low)---
- abnormal—true
- abnormal: **false**(false positivity)
- 增加—恶化
- 減輕:改善



1. Lab data 常是診斷的依據

- 一個datum→ 一個病:或問題(potential or presenting problems, even emergency)
- AFP > 10,000 ---→ hepatoma (DD時代)
  >400---------→ hepatoma
- HBsAg (+) ------→ HBsAg carrier
- GPT> 300------→ liver cell necrosis
- Triglyceride > 300-→Hyper-triglyceridemia
- Lipase > 2,000---→ acute pancreatitis
- Glucose < 40----→ hypoglycemia

疾病代表狀態及危急性

- hypoglycemia ---立即治療否則 coma→ 死亡
- Abnormal CEA→意義 **false (+)** or true (+)
  What kinds of pathology related :要去找
  很多 **cancer** 早期並無症狀.
- HBsAg (+) 一生要注意的問題 –liver disease→ cirrhosis →HCC.(LONG TERM PROBLEM)
- Lipase 高→ Acute pancreatitis或輕或重,或生或死/全靠是否處置得宜

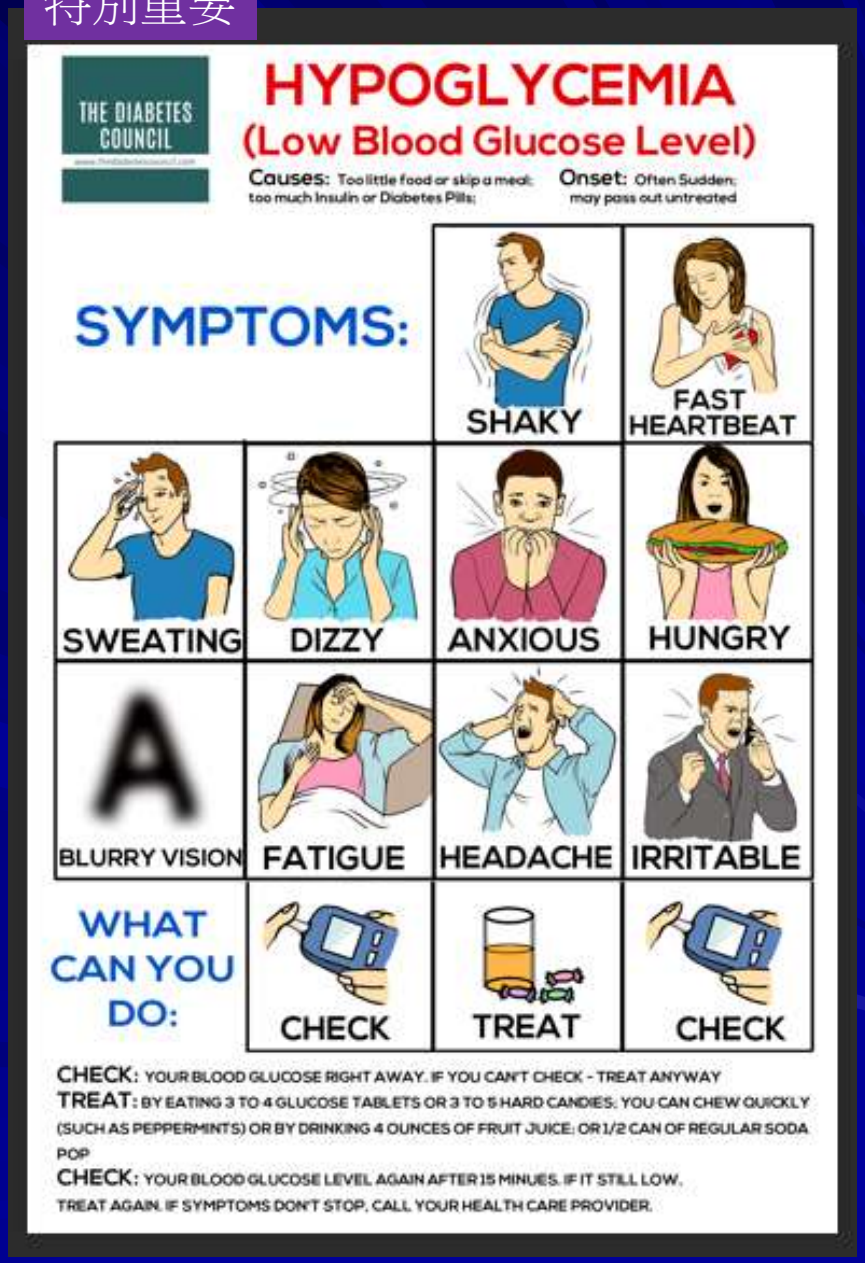
Hypoglycemia

特別重要

What are the symptoms of low blood sugar?

Symptoms of low blood sugar can occur suddenly. They include:

- blurry vision
- rapid heartbeat
- sudden mood changes
- sudden nervousness
- unexplained fatigue
- pale skin
- headache
- hunger
- shaking
- dizziness
- sweating
- difficulty sleeping
- skin tingling
- trouble thinking clearly or concentrating
- loss of consciousness, seizure, coma



Treatment of hypoglycemia

Treatment of Hypoglycemia

Conscious Patient	Unconscious Patient

★Hypoglycemia is an emergency and needs to be treated **immediately**

- Give the patient 15-20 grams of quick acting carbohydrate
  - ✓ 4-6 oz Regular soda
  - ✓ 8-10 Candies
  - ✓ 4-6 oz Orange Juice
- Repeat in 15 minutes if no improvement
- Longer acting carbohydrate
  - ✓ Crackers with peanut butter or cheese

★ Immediate notification of health care provider especially if symptoms do not subside

- Subcutaneous or IM injection of 1 mg Glucagon
- IV administration of 50 mls of 50% Glucose

Follow up blood sugar after treatment within two hours→then-----

1盎司（Ounce）等於28.35公克（gram），

4-6 oz= 113, ~170 ml. 一大杯

Hypoglycemia, 症狀variable

- 覺得奇怪,
- Hypoglycemia 的可能性-→Check,.
- Insulin over dose, medication over dose)
- Repeated dose （忘了以為沒有打針，再打一次).
- Over Exercise 忘了吃東西
- No food before another dose)

2.代表disease的嚴重度(合併症)

- 1. WBC > 15,000 severe infection
  > 30,000 leukemoid reaction
- 2. CRP >8 severe inflammation
  severe tissue destruction
- 3. CEA >30 : advanced cancer(? METASTASS)
- 4. T. bilirubin > 2.0 decompensate cirrhosis
- 5. Serum ca < 8.0 mg/dl : necrotizing pancreatitis
- 6. Prothrombin time：> 20 sec: **severe bleeding tendency—liver failure(poor outcome)**

7. NH3 > 180 – hepatic coma,

3.指出疾病的線索(診斷及原因)

- 1. **TG > 2,000-→** acute pancreatitis due to hyperlipidemia.
- 2. Hyperamylasemia + increased lipase
  → acute pancreatitis
- 3. Severe anemia +microcytic anemia
  (MCV < 80)→Chronic bleeding (GI? Hemorrhoids, menstruation?)→ colon cancer.
- 4. **Bilirubin 0.2/2.0** → hemolytic process.
- 5. GGT >200 :obstructive jaundice or alcoholic liver disease.**(GGT: biliary enzyme)**

Anemia (blood pictures 相同)

- Age, sex and historical presentation.
- Young female with menstrual problem (hypermenorrhea) →anemia
- Old age, man, with pallor of the face and symptoms of severe anemia →colon cancer at the right side colon.
- **Young man with history of IBD** (UC) : frequent bloody diarrhea and severe anemia

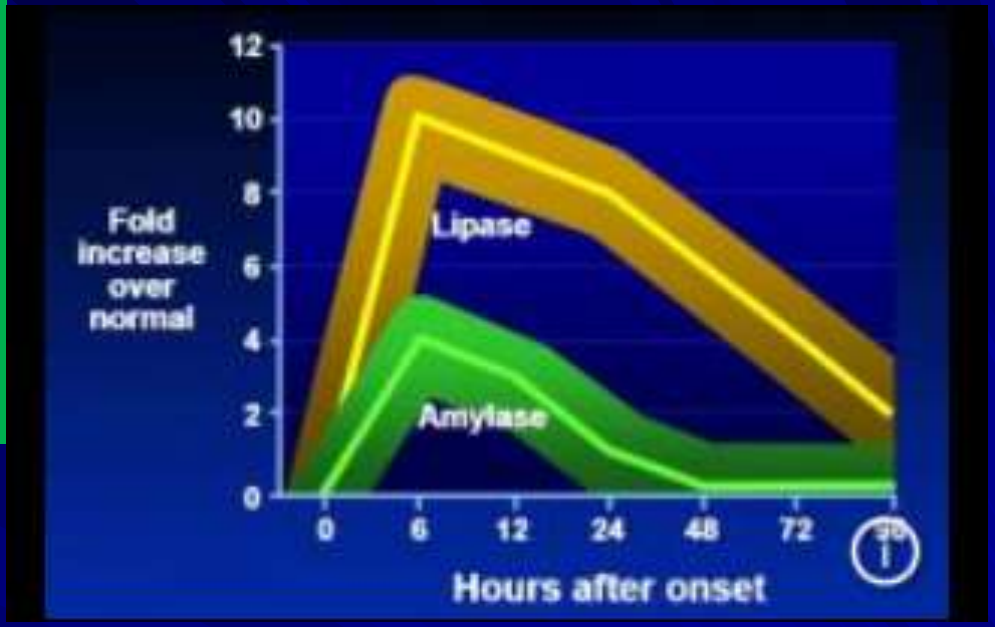
4. 檢驗數據可以判定治療之效果/特殊問題(predictive value)

- 1. CRP abnormal data → 減少→ normal
- Improved, 改善
- 2. CEA 由 abnormal 變 normal, Improved,
- 改善, 或原因消失 (smoking)
- 3. Hb : 增加 , Hb 8.0增至 12, Effects of blood transfusion + 出血已停止
- 4. Total Bilirubin :黃疸色素 下降 → normal, improved, 改善. Obstructive jaundice after ERCP and papillotomy.

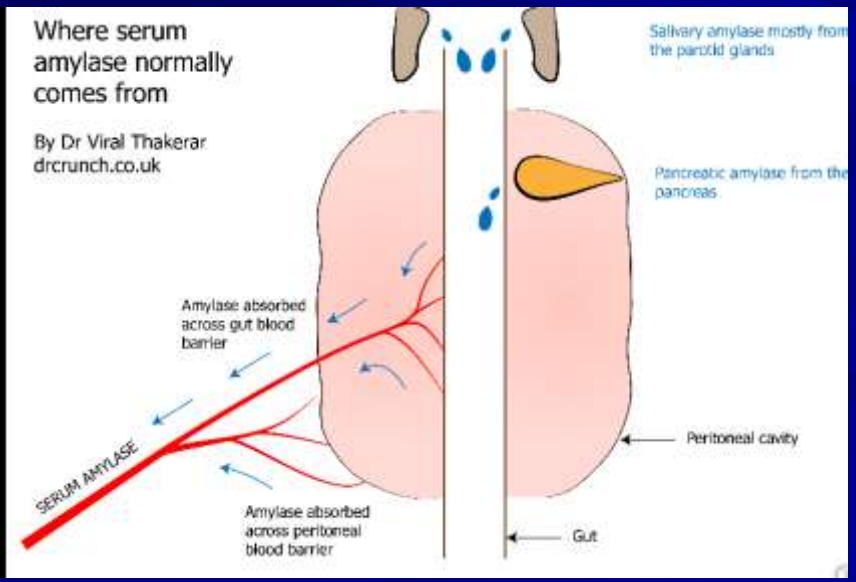
5. Natural course 之變化?

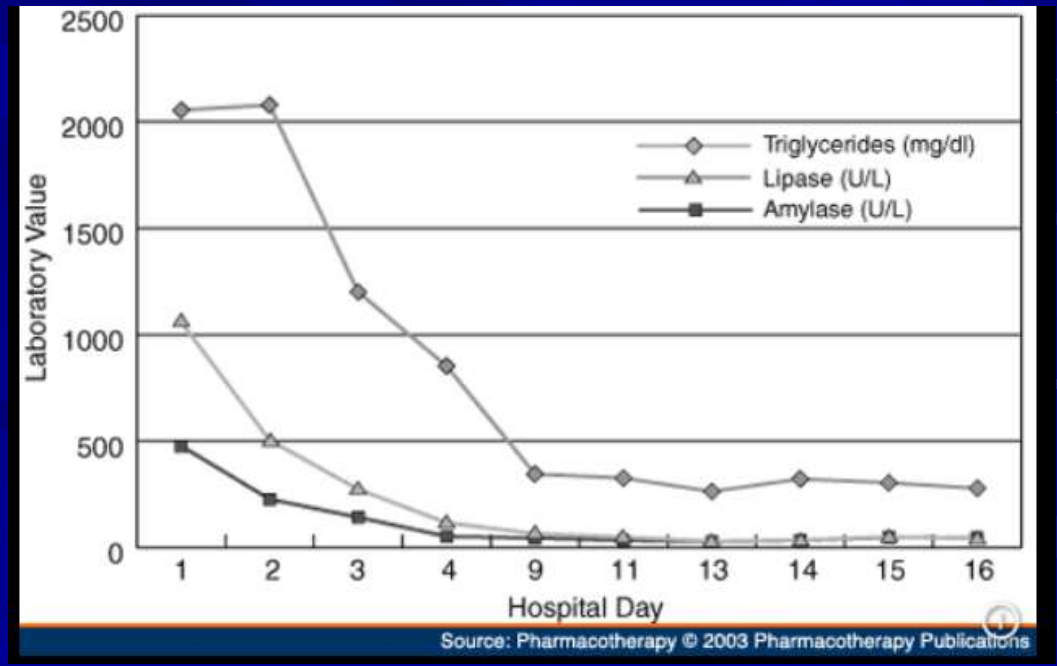
- Serum amylase : 1200 U (on the second day)
- Serum amylase : 160 U (on the fourth day of AP)
- (1) acute pancreatitis 之後已慢慢改善
- (2) 入院之後未喝酒,致病原因消失
- (3) Gall stone impacted at CBD → relieved after papillotomy, 治療有效.
- **Timing of lab examination(發病後第x天)** and also **interpretation** 需考慮各種狀況(**not only one reason.)**

Amylase and lipase in acute pancreatitis



TG >1,000mg/dl might be cause of Acute pancreatitis





Difficulty of diagnosis of acute pancreatitis beyond 3 days

- Usually serum amylase became normal.

Timing.
Time : Onset of disease.

- Urine amylase was still abnormal.
- Total daily urinary amylase output > 8,000 U.
- Amylase/ Cr. Clearance ratio > 3.0 if no renal disease.
- Lipase was still abnormal.

Amylase/Creatinine clearance ratio

What is the Significance of the Amylase/Creatinine Clearance Ratio Blood and Urine Test Result?

The significance of the Amylase/Creatinine Clearance Ratio Blood and Urine Test result is explained:

- A high test value may indicate:
  - Pancreatitis
  - Diabetic ketoacidosis
  - Renal insufficiency
  - Duodenal perforation
  - Pancreatic cancer
  - Myeloma
  - Light chain disease
  - Urinary obstruction
  - Kidney disease, including acute and chronic kidney failure
  - Acromegaly
- A low test value may indicate:
  - Anemia
  - Muscular dystrophy
  - Severe liver disease
  - Macroamylasemia

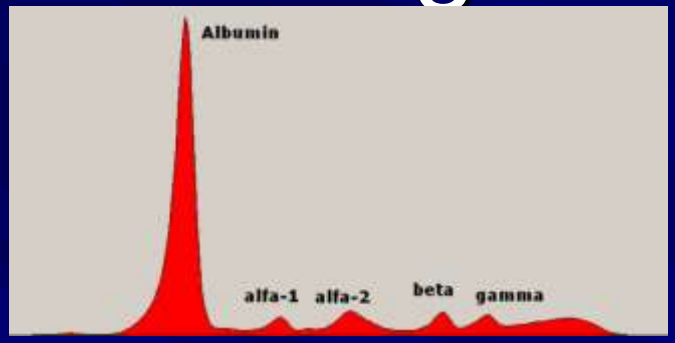
$$\frac{\text{Amylase clearance}}{\text{Creatinine clearance}}(\%) = \frac{\dfrac{[\text{urine amylase}]}{[\text{serum amylase}]} \times \text{urine volume per unit time}}{\dfrac{[\text{urine creatinine}]}{[\text{serum creatinine}]} \times \text{urine volume per unit time}} \times 100.$$

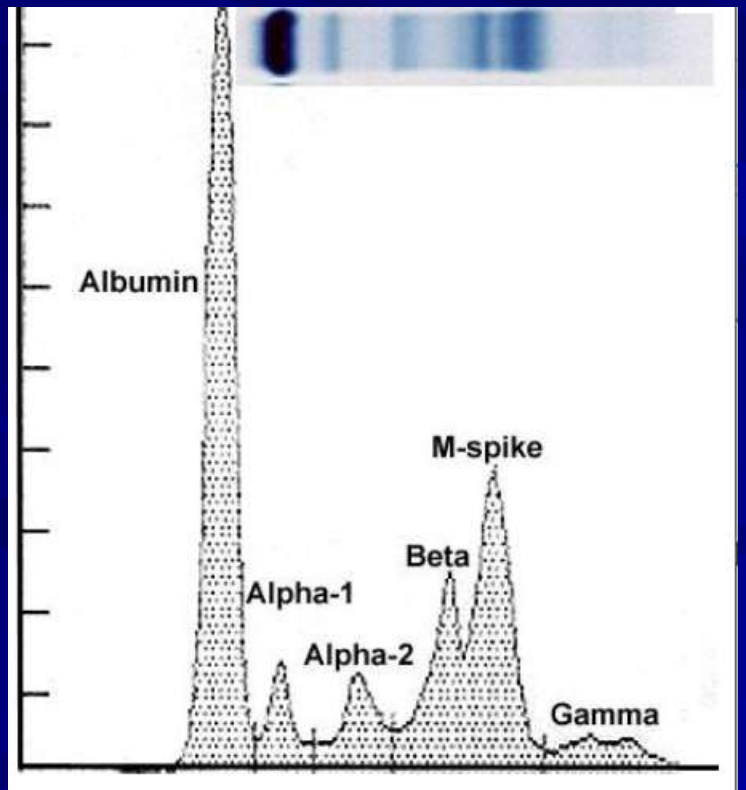
$$= \frac{[\text{urine amylase}]}{[\text{serum amylase}]} \times \frac{[\text{serum creatinine}]}{[\text{urine creatinine}]} \times 100.$$

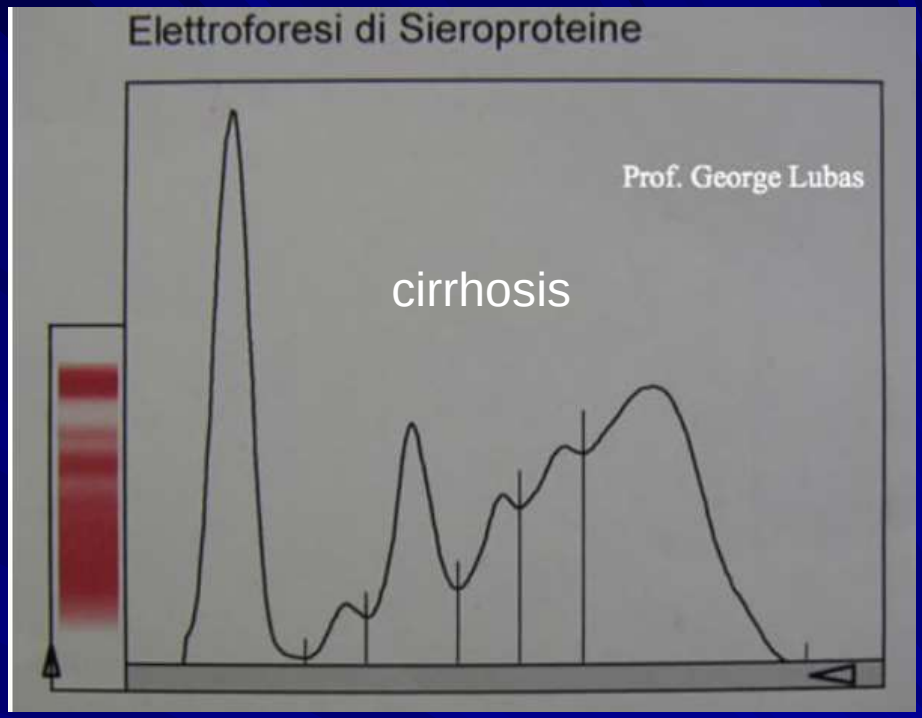
6, 綜合各個數據以判斷 cirrhosis

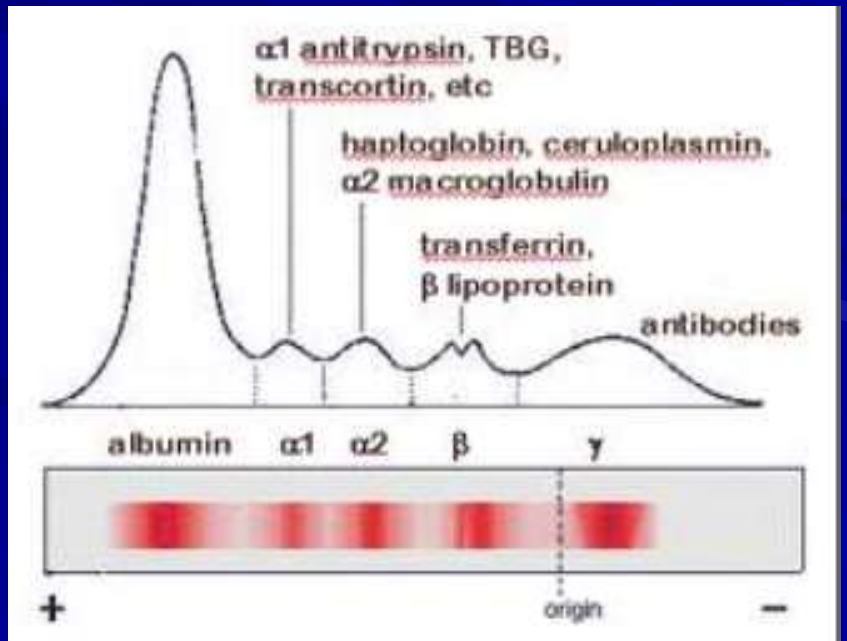
- Leukopenia < 3,500
- Thrombocytopenia : < 120,000
- **A/G reversed** : alb : <3.3 gm/dl, Glo: >3.5
- Beta-gamma linkage –protein electrophoresis
- **Mild bilirubinemia : >1.2 but less than 2.5**
- GOT>GPT (ratio : >1.0~2.0)

Beta-gamma linkage



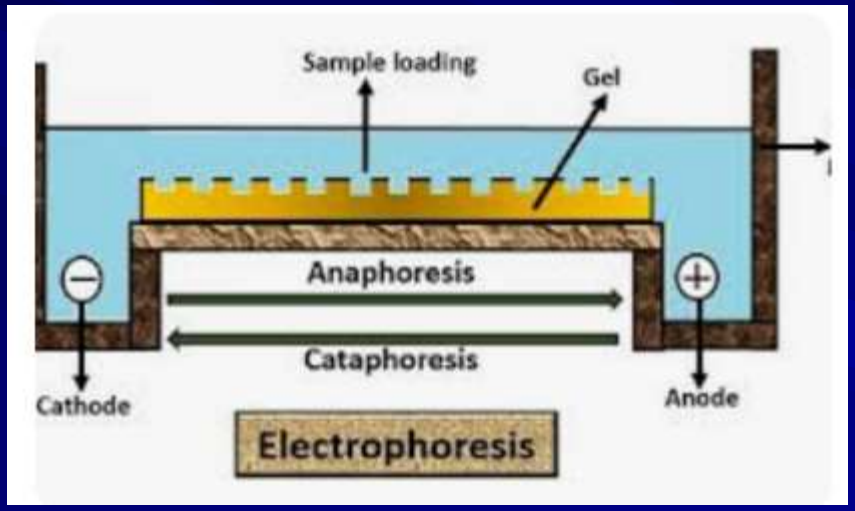


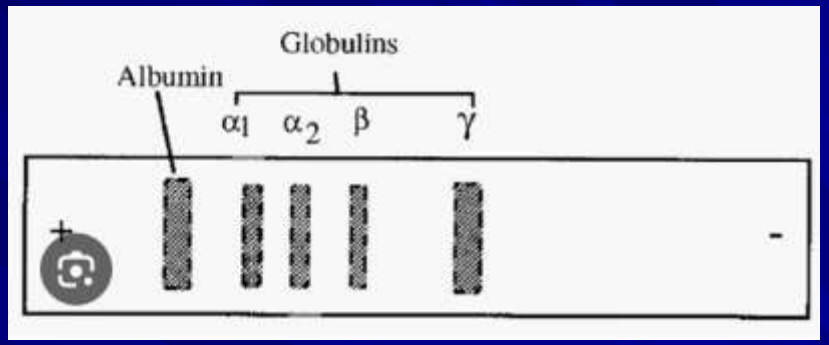


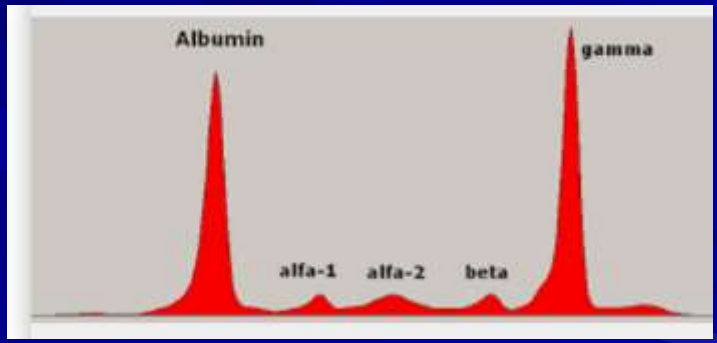


Cirrhosis + HCC ? (3 %/yr)

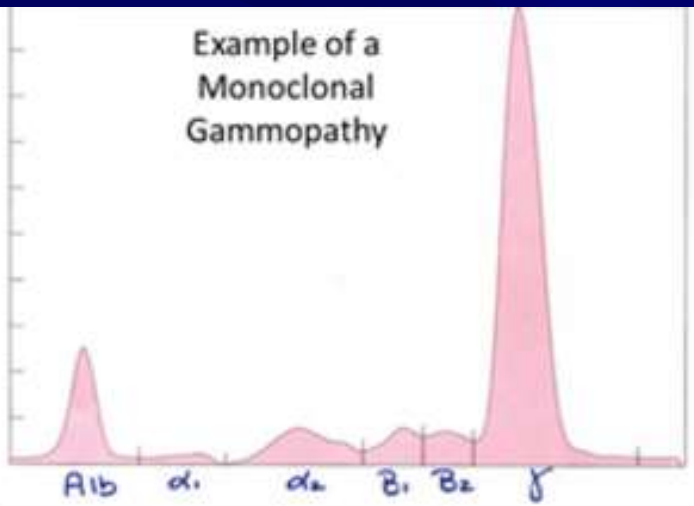
- Typical patterns of liver function tests
- A. Cirrhosis---hyper-bilirubinemia, mild
- direct bilirubin >0.4,<2
- total bilirubin>1.2,<4
- SGOT>GPT ratio(1~2))
- A/G : reversed, Alb<3, Glo:>3.5
- Pro-thrombin time: prolonged. >14sec. <18sec.
- B.HCC---------GGT>150 (3-10倍)
- -------ALP>1.5倍
- SGOT/GPT: >3.
- worsen rapidly (bilirubin increased)


Sample loading
Gel
Anaphoresis
Cataphoresis
Cathode
Anode
Electrophoresis


Globulins
Albumin
α1 α2 β γ
+
-


Albumin
gamma
alfa-1
alfa-2
beta

Monoclonal gammanopathy



Parameter	Results	Reference Interval
Total Protein (g/dL)	13.9 H	5.3 – 7.0
Albumin (g/dL)	1.95 L	2.19 – 3.29
α1 (g/dl)	0.18	0.1-0.31
α2 (g/dl)	1.22	0.94-1.63
β1 (g/dL)	0.56	0.34 – 1.01
β2 (g/dL)	0.48	0.21 – 1.03
γ (g/dL)	9.52 H	0.34 – 1.09
A/G	0.16 L	0.51 – 1.14

- Total protein:13.9
- Alb : 1.95
- Globulin :11.95
- A/G : 0.16
- Gamma globulin : 9.52

Monoclonal gammopathy
By Tracy Stokol / February 12, 2014

Protein fraction

- A/G reversed in cirrhosis
- G. increased rapidly after attack (10-14 days) by Kunkel test (in CAH)
- Serum protein electrophoresis – beta-gamma linkage→ cirrhosis
- Ig G / **IG G4** increased in autoimmune diseases, AIP----
- Rapid reduction of serum albumin in AH-→ severe liver failure

區別acute和chronic hepatitis

TABLE II.—Distribution of Zinc Sulfate Turbidity Values in Pathological and Normal Sera

Sera	Percentage of sera with turbidity in the range 0 - 5	6 - 10	11 - 15	16 - 20	20
Pathological					
—hyperproteinemic, paraprotein	34.4	12.5	9.4	10.9	32.8
—hyperproteinemic, no paraprotein	8.3	26.2	27.8	26.2	11.5
—normoproteinemic	64.9	33.3	1.8	0.0	0.0
—hypoproteinemic	94.4	0.0	0.0	0.0	5.6
Normal	93.0	6.0	1.0	0.0	0.0

Summary Comparison of the zinc sulfate turbidity with the protein level in 200 pathological sera was used to predict the presence or absence of paraproteinemia. Prediction was correct in 84.5% of the cases. Seven cases of paraproteinemia out of 68 were not detected by the technique.

It is suggested that the zinc sulfate turbidity test, combined with protein determination, provides a valuable screening test for paraproteinemia.

- ZTT > 16 indicated Presence of paraproteinemia

--→Indicated chronic change.

- **Acute hepatitis 出現gamma globulin通常是4週之後.**
- **chronic hepatitis with acute exacerbation 在2週之內即出現**

7.代表病人的配合度不好

- **Hb A1C . >8.0: DM 病人DIET CONTROL** 不好
- UC : CRP > 3.0 – relapsed.

  No medication

  Increased stress or busy or heavy meal
- **CEA: 增加** (6.0→ 12) in smoker: 再抽菸
- **GGT : 30--→ 103 in drinker** 又再喝酒了
- Glucose 又降至40 mg/dl 以下:

  Ex. 注射insulin, 沒有吃食物.,

  insulinoma.

Peculiar case example
不一定用normal variation來解釋

- Aged 88 male, ex-smoker for 20 years.
- CEA : increased definitely up to 7
- Reviewing his smoking history: no more smoking for 20 years but **exposed to a heavy smoker in the park** every morning during exercise.→ recheck CEA→still high.
- Chest X-ray and chest CT showed a small **mass 1.0 cm., in size**. It was then resected. CEA down to normal after operation.

Elevated CEA in cancer patients

- Key points：在解釋 abnormal data
- True (+) or false (+)
- false (+)的條件?
- 不妨 查Chest X-ray and CT.
- Follow up.

- **High False-Positive Rate of Elevated CEA Seen in Patients With Resected Colorectal Cancer**
  By Charlotte Bath August 15, 2014
  The ASCO Post
- *Litvak A, et al: J Natl Compr Canc Netw 12:907–913, 2014.)L1543)*
- *1.* 49% false-positive of carcinoembryonic antigen (CEA)
- 2. **Confirmation of an ongoing increase in CEA level should be universal practice** before an extensive workup is initiated,

CEA: abnormal in cancer patients (L1543,L1544)

- 728 cases of CRC
  Memorial Sloan Kettering who underwent resection for stage I, II, or III colorectal cancer between 2003 and 2012, and who had an increase in CEA level above the normal after a normal perioperative CEA level.
- 358 had a **false-positive** elevation of CEA level,
- 335 had a true-positive elevation indicative of **recurrent** [colorectal cancer],
- 35 had a true-positive elevation indicative of the development of a **new**, [non–colorectal cancer] malignancy,"

- **1. no evidence of cancer on either imaging studies** or other diagnostic procedures,
- **2. follow –up** of (1) **at least 1 year** since the first abnormal CEA or
- (2) abnormal CEA elevations followed by **spontaneous normalization,**
- **(3)** with at least **2 consecutive subsequent normal CEA** measurements in the absence of a therapeutic intervention,

- @@@ 247 patients with 2 or more confirmed false-positive CEA level elevations, only 5 (2%) had measurements greater than 15 ng/mL, and no confirmed elevation greater than 35 ng/mL was a false-positive,
- FALSE (+) 很少 >15,
- False (+) 不會超過 35

Same conclusion in 1977, Special lecture
False (+) often around 5-10, rarely > 15,
IT was definitely abnormal when CEA>20

8.代表治療反應好或不好

Improvement　轉好

- 1. CRP　減少
- 2. WBC　return to normal
-
- 3. Amylase return to normal
- 4. Hb: 增加/貧血改善,
- 　出血停止

Downhill效果不好

- 1.CRP 增加
- 2.Leukocytosis.
  Leukemoid reaction
  WBC增加
- 3. relapse of pancreatitis
- 4. 減少, 貧血加重或繼續出血

很好的 assessment parameters

怎樣選assessment parameters

與vs多一些討論就可以有概念
每一個案例都要思考病情於指標之間的關係and

- 對疾病深入瞭解,
- 善於利用各種 lab data
- 發病日(期間,staging) 會影響改變
- Normal or abnormal.
- Individual variation個別差異/治療之影響
- 挑本**案例差異**(不正常)最明顯的項目.

VS Round 時必須告知年輕的醫師
怎樣選評估指標

那個檢查最能看出疾病之進行 disease activities

- Presenting symptoms and data –症狀依舊 病人覺得不舒服,沒力氣, 胃口沒有改善----
- Tumor markers– CEA,
- UC :Inflammatory parameters– ESR,CRP, and WBC.
- Hypoglycemia—sugar, symptoms.
- Hypokalemia –K, ECG
- Acute necrotizing pancreatitis :Ca. CRP and lipase

9. 檢驗錯誤或 false positive Ex. CEA

- 1. CEA – 5~ 10 --→smoker ? Or other condition
- 2. EIA or RIA
- EIA ---data 穩定性不夠， RIA：比較可靠
- 3. 增加 -→ Lab error ?，Cancer 更厲害，未控制住，吸菸故態復萌
- 4. > 20: 可能已有 metastases.
- 5. 不同醫院不同的 **Lab.** 不宜直接比較(但可以參考)(因為檢驗方法不同)

10. 好好思考、紀錄、處理

- 跟 Present illness 的關係
- 1. Diagnostic evidence
- 2. Indicates severity
- 3. Indicates therapeutic response
  better or worse.
- 4. **Associated diseases.**
- 5. Treatment regimen. Change or modify.
- 6 Express the opinion at recording of the lab data

11.基本的檢查項目一定要熟習
(a) normal range (b)臨床意義

- CBC, differential counting,
- blood smear,
- Urinalysis
- Stool examination, OB, Parasite, Fat
- **LFT: GOT, GPT and GGT---**
- RFT : BUN, Cr, **UA**
- Electrolyte: Na, K Cl. and Ca,
- CRP
- AC sugar, PC, and Hgb A1c
- Arterial blood gases analysis

- Normal range
- Clinical significance
- Critical value
- How to manage.
- Diagnosis
- Screening
- Outcome.

11.基本的檢查項目-原則(二)

- 一定要很熟悉,各種狀況都知道(Dx and DD)
- Normal ranges
- Interpretation:

  Definite, --diagnosis

  Possibility of abnormalities各種可能性:

  False positive之情形
- 記載結果及評估-→一定記入病歷
- 即時處理/立即處理(訂定工作規範、電腦上及時顯現處置方式、)

(三)Data要處理: 1.處理的種類-極端值

- 1.極端值---危險值/判斷是True or false
- True---立即處理,有相關的症狀,
- 立即治療務必改善,治療後,追蹤檢查
- →判斷已改善/未改善
- @. Sugar:25mg/dl----cold sweating + palpitation-→hypoglycemia-→IV glucose-→better after treatment—recheck sugar
- @Serum K:2.2mEq/L---無症狀但 ECG 有變化, IV drip補充-→better after treatment仍要再查確定K

人好好的但是data 很糟糕, 怎麼辦?

- 你以為錯誤,而置之不理-→不可以
- Recheck data immediately

1.告知病人家屬
2. Iv route set.
3. Recheck data 大約30分鐘內就可以確定.
4.把在查的結果告知病人家屬.
5. Sudden death was noticed when hypokalemia Was noted one hour before

(三)要處理: 處理的種類2.**異常值**:
思考檢驗值**不正常**之意義並記在病歷上

- 不正常值—先知道代表的臨床意義: 本病例是否有此情形
- **疾病/合併症/病情的一部分**
- False:偽陽性之狀況
- False: Lab quality有問題—作錯
- False: Lab.檢體弄錯人
- False: 抄錯結果
- Lab error: 5 %, acceptable
- Normal variation.

兩個例子

- Total bilirubin—1.49mg/dl 代表 不同疾病
  - *Post-hepatitis hyperbilirubinemia
  - *Non-conjugated hyperbilirubinemia
- AFP: 29----------*(GOT and GPT:每3個月一次連續3年均正常,不像CAH引起,也無cirrhosis, Abd. CT and Sono也無HCC.)
  - * Unexplained increase ?
  - * **Normal variation** —increased production without disease

12.All abnormal data 要 Follow up,作為下一步處理之依據(住院病人至少每一週)

- 1. Turn to be normal – Improved, healed, better than before, effective in treatment, no more active (disease activity)
  2. Aggravated or increased--- became abnormal, worse, downhill, complicated, not effective in treatment. Still active
  3. Remain the same extent—the same condition, not effective in treatment.

13.出院前要再確認一次

- Normalized-→ treated and improved.
- Still abnormal—但已減小,改善(好很多)
- Still abnormal---未變好/甚至更高-
  →尚未好轉,
- 有未查出的問題,→ readmission reasons
- 值得注意,再 follow up.
- 絕不可置之不理或等閑視之
- Abnormal data—正代表問題或其結果

14. CBC in Cirrhosis
異常中見出特點

- Hb---- 正常或稍低
  明顯低 (Hb:<12gm/dl)—有出血史?
- WBC: 低<4500
  低於3000---Hypersplenism(>2,000)
  低於2,000---另有原因
- Platelet:低—<150,000 (100,000~130,000)
  明顯低<100,000 (50,000~80,000)
  很低---around 30,000~50,000– *Hypersplenism*
  非常低 <30,000----另有原因

15.Thrombocytosis

- **Platelet > 400,000**
- **causes :**
- **1. BM: over production**
- **2. Spleen :reduce**
- **destruction of platelet**

Thrombocytosis cause

Essential (primary)

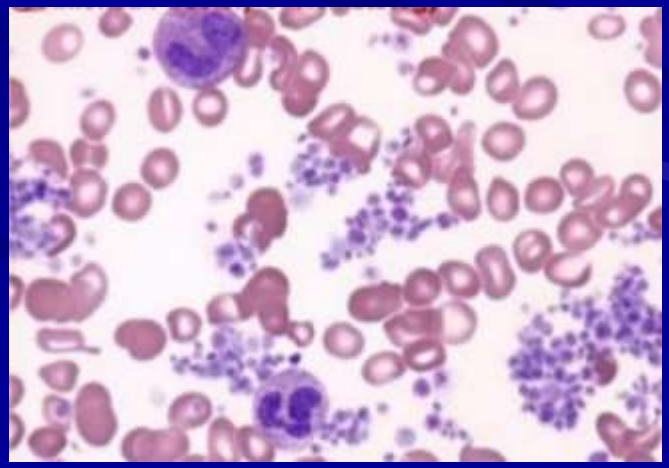
- Essential thrombocytosis (a form of myeloproliferative disease)
- Other myeloproliferative disorders such as chronic myelogenous leukemia, polycythemia vera, myelofibrosis

Reactive (secondary)

- Inflammation
- Surgery (which leads to an inflammatory state)
- Hyposplenism (decreased breakdown due to decreased function of the spleen)
- Asplenia (the absence of normal spleen function)
- Hemorrhage and/or iron deficiency

Over-medication with drugs that treat thrombocytopenia may also result in thrombocytosis

- **Refer all thrombocytosis patients for cancer check,**
- *Thrombocytosis has an 11.6% positive predictive value for cancer in men and 6.2% in women, according to research published in the British Journal of General Practice (BJGP).*
- David Millett on the 23 May 2017 at GP



16. Thrombotic tendency

- **Thrombotic tendency:** A disorder of HEMOSTASIS in which there is a tendency for the occurrence of THROMBOSIS.
- 1. Thrombocytosis
- 2. Polycythemia
- 3. Extreme hyperglobulinemia
- 4. Auricular fibrillation
- 5. Presence of cryo-globulinemia
- 6. Vascular injury (ex. During cardiac cathe,)

D-dimer為纖維蛋白分解產物(Fibrinogen degradation products)之一，當D-Dimer結果為陽性可用來診斷傳統 DIC (Disseminated intravascular coagulation)疾病；陰性時搭配臨床症狀可作為DVT (deep venous thrombosis) 及PE(pulmonary embolism)的排除診斷，結果為陽性時則需做進一步影像檢查確認是否為DVT及PE疾病

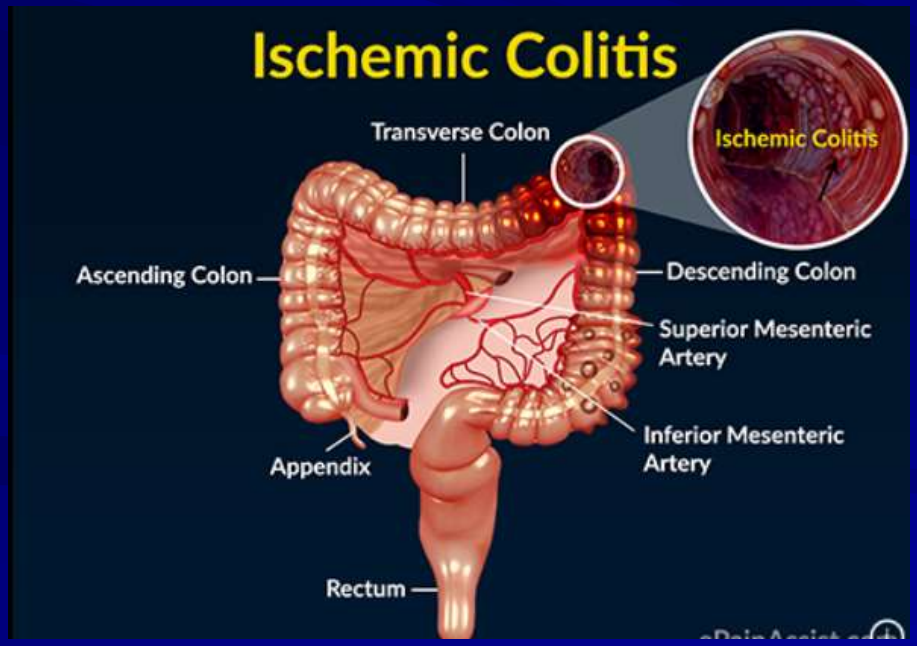
Table 1. Pathological and non-pathological conditions associated with high D-dimer levels.

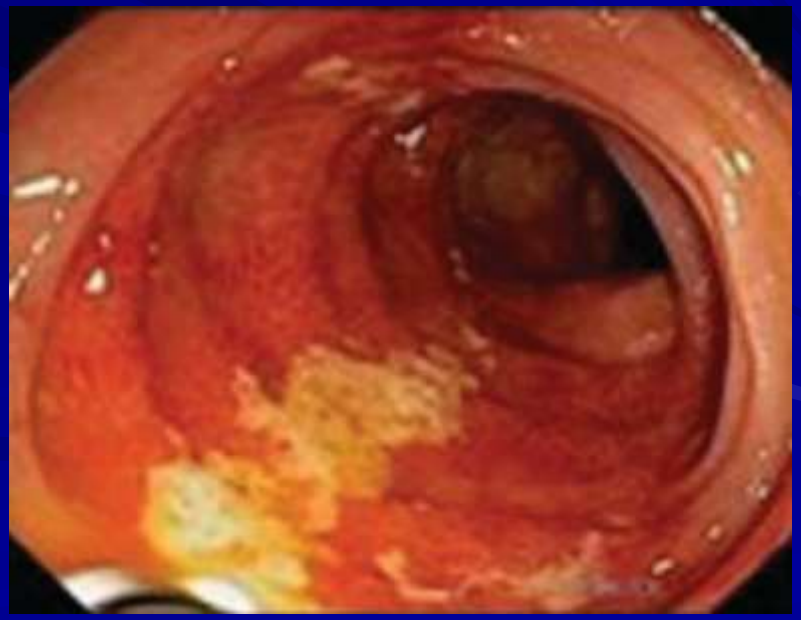
Physiological
Aging
Pregnancy
Physical exercise
Pathological
Venous thromboembolism[1]
Cancer[1]
Disseminated intravascular coagulation[1]
Cardiovascular diseases (atrial fibrillation, coronary artery disease, acute aortic dissection[1])
HELLP syndrome
Diabetes
Hemorrhages
Infections (peri-prosthetic hip and knee infections[1])/sepsis
Inflammation
Cirrhosis
Renal disease
Trauma/surgery

Massimo Franchini[1] Et al
How we manage a high D-dimer
Haematologica. 2024 Apr 1;109(4):1035-1045.
(L1513, L1514)

First case of ischemic colitis due to polycythemia

- RBC: 6,5 m
- WBC: 18,900
- Thrombocytosis: 650,000





Mesenteric infarction due to Procrit.

- **Mesenteric infarction due to iatrogenic polycythemia.** Skoog K,et al (*University of Florida School of Medicine,US):*World J Emerg Med. 2013; 4(3): 232–234.
- a patient with a history of non-small cell lung cancer undergoing maintenance oral chemotherapy on tarceva and adjunctive use of procrit. The patient presented to emergency department with an acute abdomen and was found to have ischemic bowel from unmonitored **procrit,** which lead to **hyperviscosity** of blood and mesenteric infarction. **PROCRIT（EPOETIN ALFA）注射液**
- A 50-year-old man with a history of stage IV non-small cell lung cancer. His CBC was checked on December 5, 2011 and H/H at that time was 19/58.6, and it trended up to 23/66 on December 11, 2011.
- Exploratory laparotomy showed that he had a significant amount of necrotic bowel from the sigmoid to the ileum. The operation included an enterectomy and subtotal colectomy.

19.Complete liver function tests for evaluation

- 只要任何一項出現不正常(GOT, GPT and GGT– **screening)→ complete tests.**
- Bilirubin: Total and conjugated bilirubin.
- AFP: normal or abnormal.
- WBC →leukopenia ?
- Platelet < 123,000
- Low serum albumin
- High serum globulin
- Pro-thrombin time

一定要同時查
Total bilirubin and conjugated bilirubin.
A/G ratio.

20.小便變紅是血尿?茶色尿?

- Tea color urine or hematuria一定要問清楚!
  「像血那麼紅嗎?」
- **Tea color urine+ Clay color stool --→ obstructive jaundice**

  Tea color urine (無灰色便)→一般之黃疸症

  --→*hepatitis(conjugated hyperbilirubinemia)*

  Urinalysis 可以證明有無血尿,確定診斷.

  *—定查**complete liver functions**. (AST, ALT,Bilirubin,ALP,GGT,A/G,prothrombin time---)*

Obstructive jaundice** 最早出現的變化是 **tea color urine

21.Anemia要好好查腸胃疾病

- GI bleeding—minor blood loss,
- --chronic,不一定會警覺。
- Colon cancer, right sided
- Gastric cancer, NSAID,
- Small bowel lesions, small or occult
- * **microcytic hypochromic** anemia
- 急性出血在24hours之後才維持平衡,真實的data.出血病人滿一天後一定要查
- Treatment: Blood transfusion 使Hb 達到10gm/dl以上老人家要慢慢輸血。

22. Evidence of liver cell damage, 請查原因

- 1. GOT or GPT >100 (recent 1-2 months)
- 2. GOT or GPT> 300 (mostly recent)
- 3. Change of serum bilirubin: increased
- 4. Prolonged prothrombin time
- 5. Clinical jaundice
- 6. Bleeding tendency
- 7. hepatic coma
- 8. evidence/signs of chronic liver disease

23. Evidence of obstructive jaundice

- Striking increase in GGT and alkaline phosphatase. **Biliary enzymes:要同時查Alk-P-tase及rGT可作疾病變化之指標**
- Mild or moderate hyperbilirubinemia
- Tea color urine + clay color stool
- CBD：dilated/intrahepatic biliary dilatation

  Itching

24. What kinds of changes indicate severe liver damage and failure ?

✦**A: 1. 相關數值顯示劇烈變化**：

- SGOT/SGPT：持續2-3週以上都是在300以上
- Bilirubin：直線上升，total bilirubin超過10
- direct bilirubin 超過4mg/dl
- **Prothrombin time ：延長至20sec 以上**
- NH3 ：上升
- Albumin： **急性病人降低至3.0gm/dl 以下**，特別是2.5 以下
  慢性病人降低至2.5gm/dl 以下，且出現大 量腹水

A2. 死亡交叉

- **(a)Bilirubin 上升，而SGOT/SGPT反而下**
- **降(至100以下)**
- **(b) 黃疸↑，但肝反而縮小liver atrophy**
- (c) Bilirubin ↑ // 肝反而縮小~意識變差
- (d) Consciousness 變差~
- Prothrombin time 延長
- (d) **Bilirubin ↑/ Prothrombin time 延長**

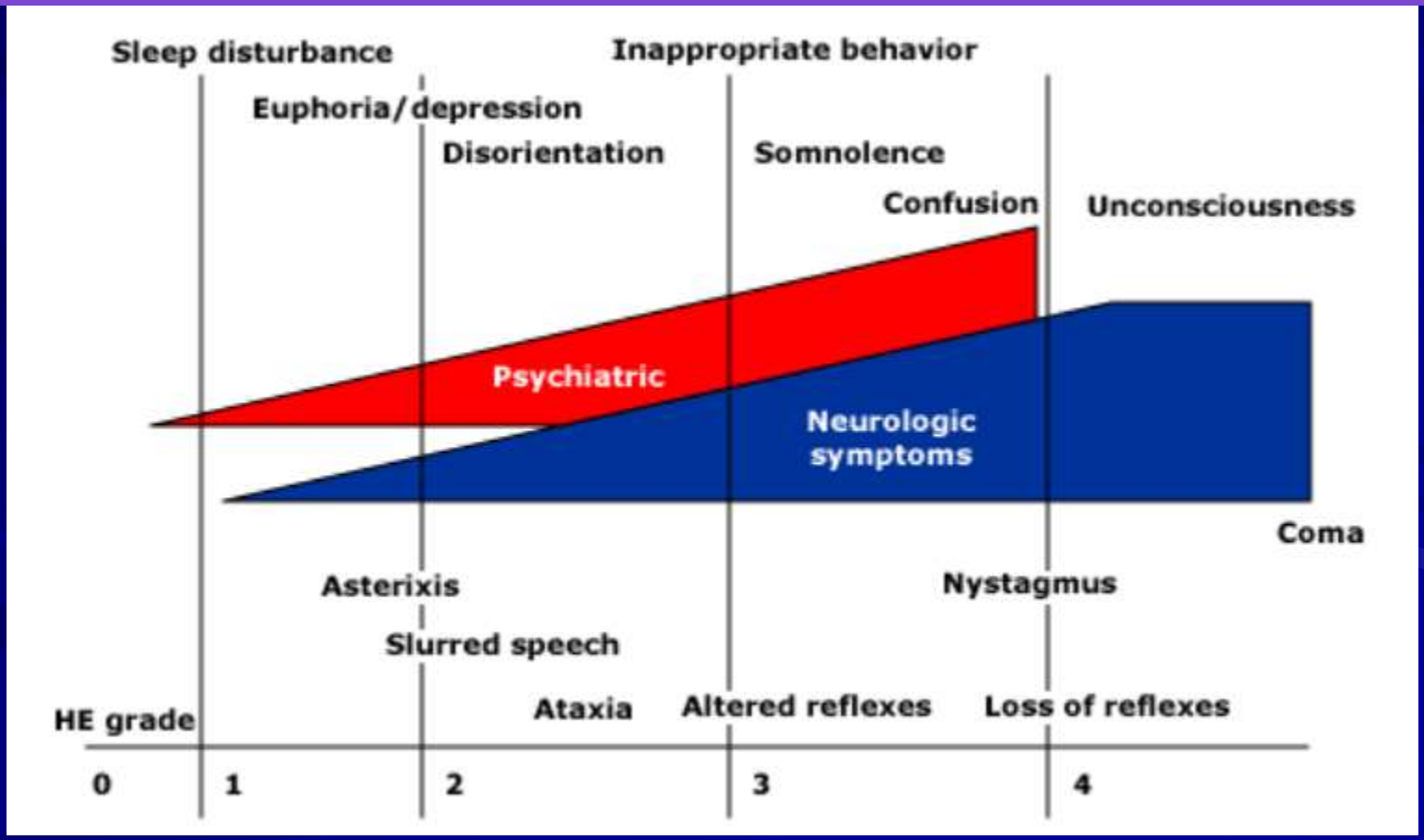
Blood ammonia

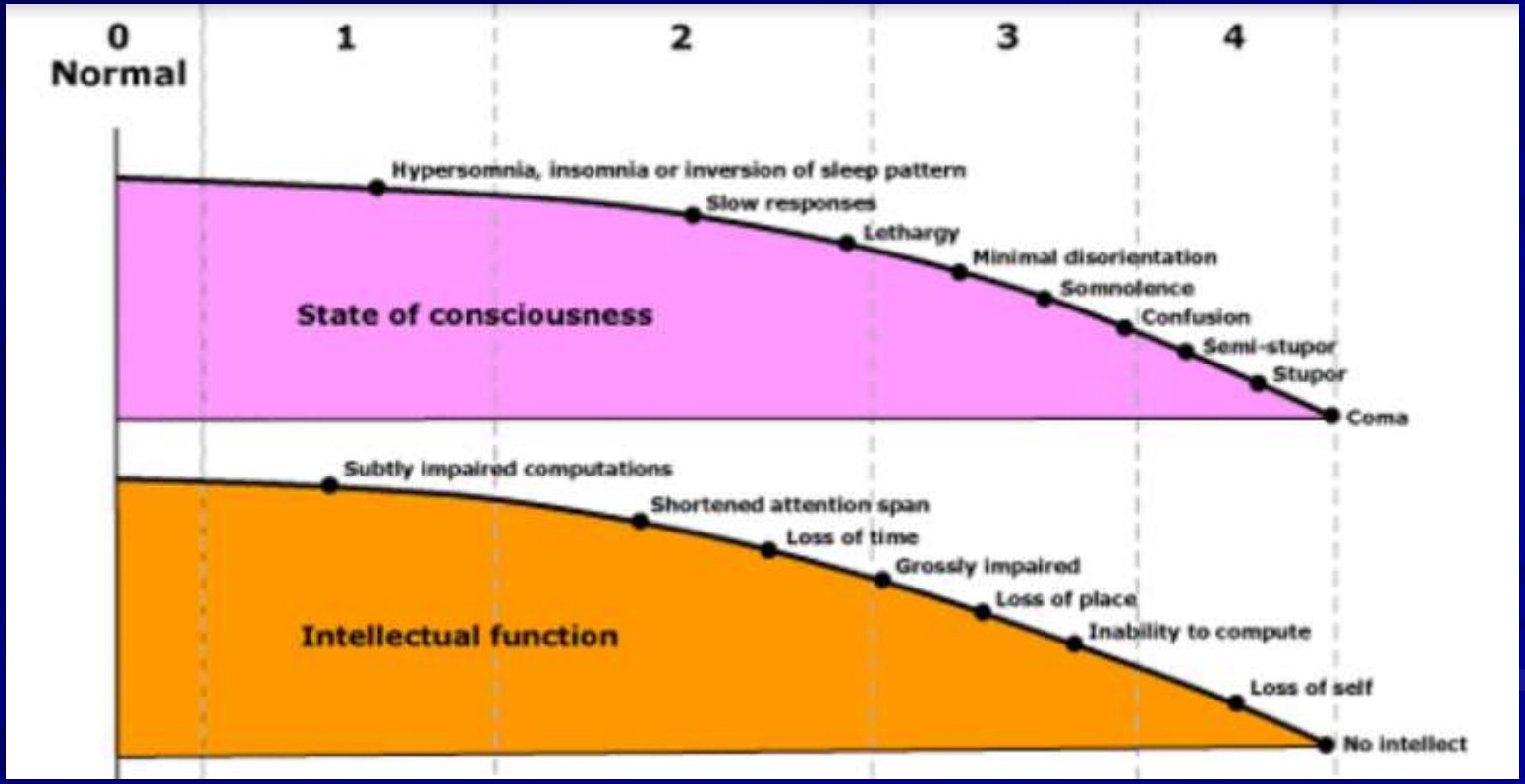
血氨濃度的正常參考值：11～35μmol/L

(**Adults**: Less than 30 micromol/L)(Cleveland Clinic)(15-60 mcg/dL in adults.)

- 氨是一種對人體有害的物質，肝臟是其主要的代謝場所。正常人血液中含有微量游離氨。內源性氨是由體內蛋白質代謝過程中產生的胺基酸，經脫氨作用分解而成，是血液中氨的主要來源。外源性氨是由蛋白質類食物在腸道內經細菌分解而成的。腦和腎臟等器官的氨與谷氨酸作用生成谷氨醯胺後被運輸到肝臟，在肝臟轉變成尿素或其他含氮化合物後由腎臟排出體外，或形成銨鹽隨尿排出。**血氨的來源增加和去路減少，都會引起血氨增高。**

- 常見一開始是睡眠混亂, 然後才是一系列神智變化, 像是行動變慢(bradykinesia), asterixis(撲翼性震顫) (手掌背曲拉筋會發生拍動的動作), DTR(肌腱反射)增強, 有時甚至會出現去大腦姿勢(少見)



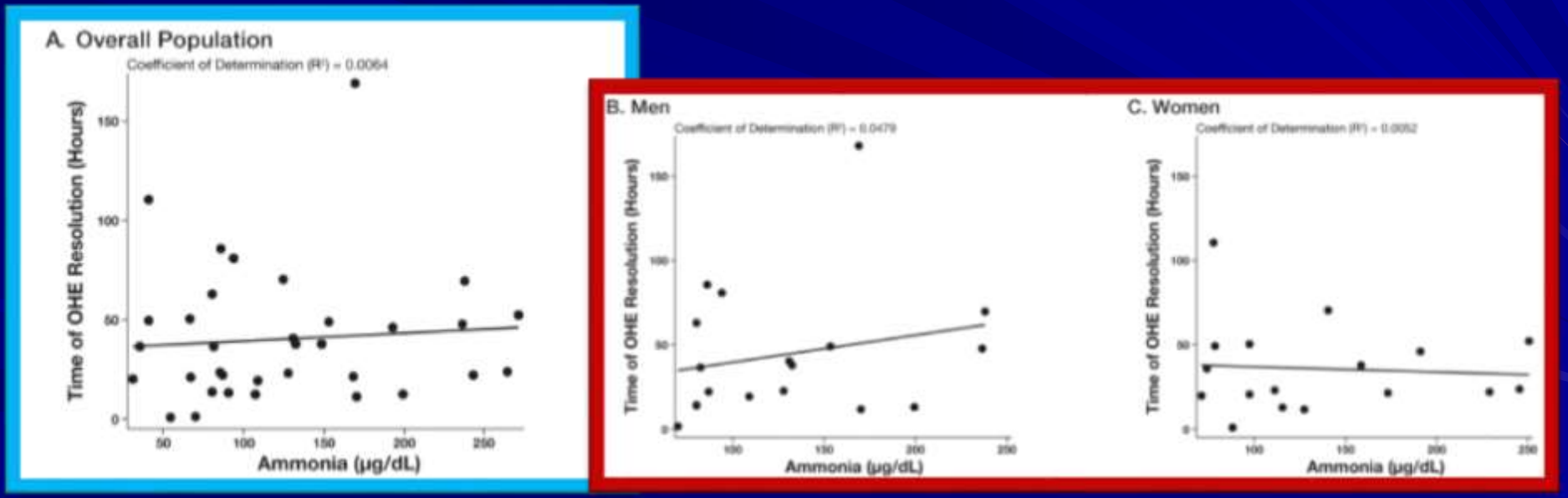

0
Normal
1
2
3
4
State of consciousness
Hypersomnia, insomnia or inversion of sleep pattern
Slow responses
Lethargy
Minimal disorientation
Somnolence
Confusion
Semi-stupor
Stupor
Coma
Intellectual function
Subtly impaired computations
Shortened attention span
Loss of time
Grossly impaired
Loss of place
Inability to compute
Loss of self
No intellect

Serum Ammonia Levels Do Not Correlate With Overt Hepatic Encephalopathy Severity in Hospitalized Patients With Cirrhosis

Jasmohan S Bajaj[1], et al ([5] Department of Medicine, Virginia Commonwealth University, Central Virginia Veterans Healthcare System, Richmond, Virginia

J Clinical Gastroentero Hepatol 2024 Sep;22(9):1950-1952.e1.

儘管氨與肝性腦病（HE）的病理生理學有關，但在臨床實踐中使用氨水準是有問題的。[1-3]例如，在一項對551名接受Lactulose 治療的顯性HE（OHE）患者進行氨水平檢測的研究中，只有60%的患者氨水準升高（定義為 >72 μmol/L）。[2]總體而言，在乳果糖劑量與是否獲得氨水平之間（即，存在/不存在氨水準升高不能指導治療）之間或 OHE 消退時間與氨水準之間沒有觀察到相關性。[2]此外，樣品處理和加工的實驗室間差異很大，這可能會影響氨的測量。



25. Acute liver failure
找原因及去除原因最重要

- Acute liver failure:
- 立刻找出原因及去除原因
- **1.**急性**B**肝→HBIG, Antiviral + supportiveTx.
- 2.Drugs---Dc responsible drugs
- 3.Alcohol-→DC alcohol
- 4.Acetaminophen –antidote
- 5. Others: unknown---**treat and observe.**
- @@Treatment of hepatic encephalopathy
- @@Liver transplantation

26. What kinds of changes indicate chronicity ?

- 1. **Globulin was abnormal, more than 3.5**
- **gm/dl.**
- 2. A/G was reversed. (in cirrhosis)
- 3. **SGPT was often more than SGOT**.
  especially GOT was normal
- 4. Globulin fraction increased greatly within 2 weeks after acute liver damage. It might be noticed by Globulin value or **ZTT**(Zinc turbidity test or Kunkel test)

27 What kinds of changes indicate **HCC** in the patients with chronic liver diseases.

1.Sudden deterioration of liver function—with jaundice– etc.

- 2. RUQ pain with hepatomegaly
- 3. Bloody ascites.
- 4. **Increase in AFP** without recent severe liver cell damage
- 5. SGOT/SGPT ratio : more than 2.5
- 6. Chronic HBV liver disease or chronic HCV hepatitis associated with alcoholic liver disease.

28.B肝帶原的病人:好好關心他的過去→HCC可能性

- Case1. 媽媽帶原? 但是**3個兄弟都有 HCC**表示媽媽帶原很明顯,

HBV→Chronic liver diseases→LC→HCC

15 years ago (at 35)---知道肝功能不正常,有 chronic changes

5 years ago---有liver cirrhosis(因 gall stone 手術)

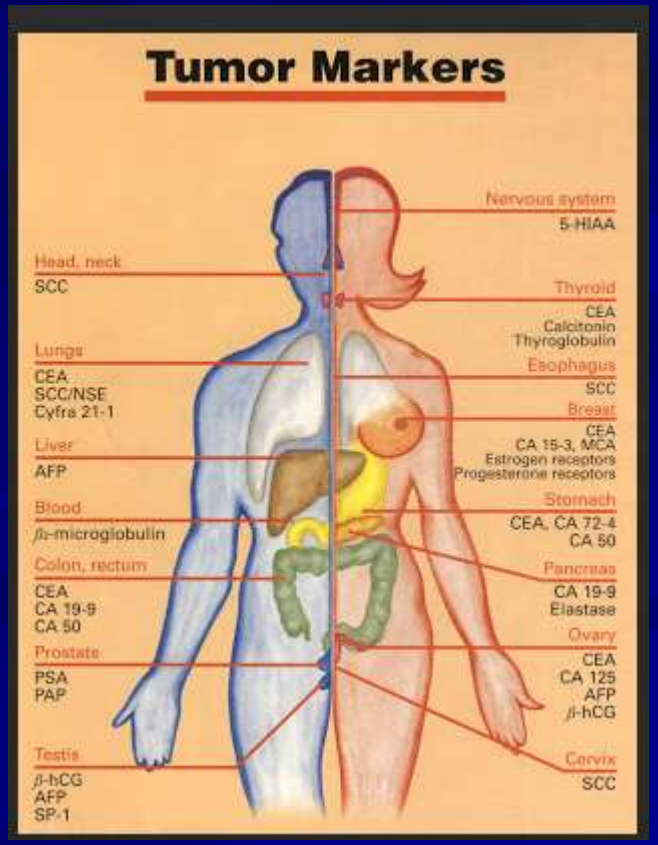
現在 **LFT 有問題: GOT /GPT=210/44 AFP>40 (44)**

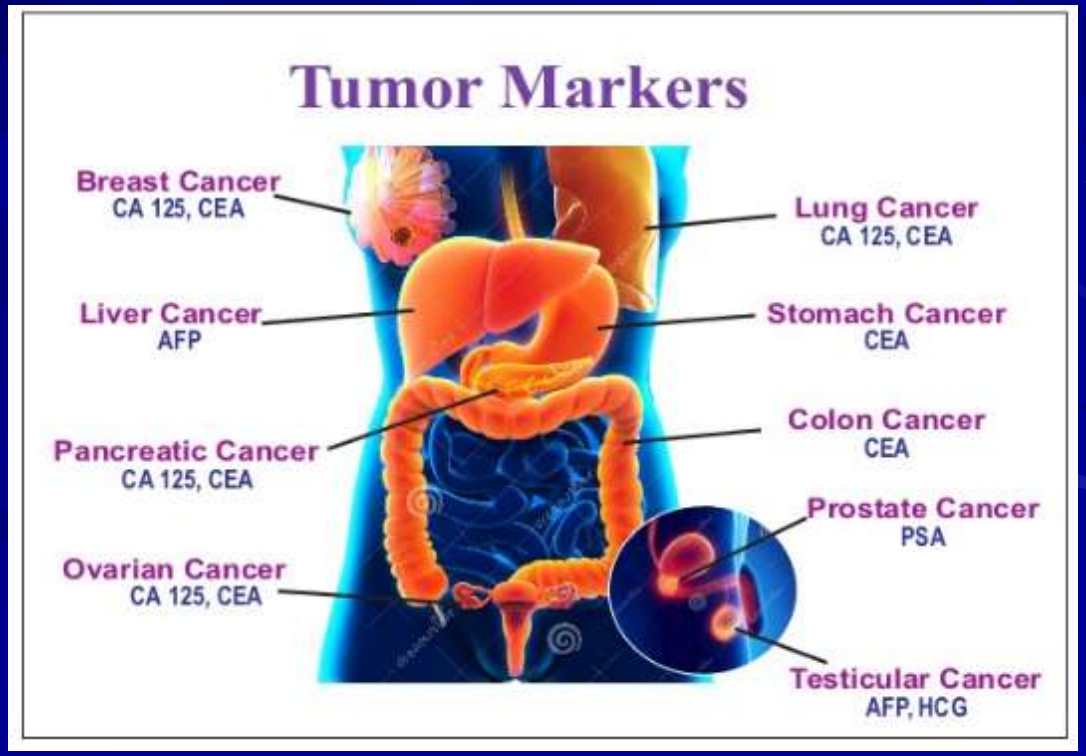
Abdominal sono– liver mass noted.

重要里程碑:Universal HBV vaccination in Taiwan from July, 1986. (age factor)

29. Tumor markers：not 100 % sensitive and also not specific

- CEA: 40-44 % for CRC
- AFP：about 70 % for HCC (abnormal)





一個tumor marker不只代表一個器官的腫瘤

Serum Tumor Markers	
Marker	**Associated Cancers**
α-fetoprotein	Hepatocellular carcinoma, nonseminomatous testicular germ-cell tumors (yolk sac tumor)
β-human chorionic gonadotropin (hCG)	Trophoblastic tumors, choriocarcinoma
Calcitonin	Medullary carcinoma of the thyroid
Carcinoembryonic antigen (CEA)	Carcinoma of the lung, pancreas, stomach, breast, colon
CA-125	Ovarian cancer
CA 19-9	Pancreatic cancer
Placental alkaline phosphatase	Seminoma
Prostatic acid phosphatase	Prostate cancer
PSA	Prostate cancer
S-100	Melanoma, neural-derived tumors, astrocytoma
Tartrate-resistant phosphatase (TRAP)	Hairy cell leukemia

Tumor markers

TABLE Tumor markers in ovarian masses

Tumor marker	Ovarian neoplasm
CA-125	Epithelial ovarian cancer
CEA	Mucinous ovarian cancer
HCG	Embryonal carcinoma Choriocarcinoma
Inhibin A or inhibin B	Granulosa cell tumor
Lactate dehydrogenase	Dysgerminoma
α-Fetoprotein	Endodermal sinus tumor Embryonal carcinoma

Abbreviations: CEA, carcinoembryonic antigen; HCG, human chorionic gonadotropin.

- 1.注意 normal ranges
- 2.causes of elevation
- Benign, false positive
- 3.注意 follow up.
- 4.不同的 histology ,有不同的tumor markers,
- 5.尚待發掘new and ideal tumor markers.
- 6.找到原因.

30, What are **decompensate signs** of liver cirrhosis(hepatic failure)

- 1. Jaundice – serum bilirubin不正常
- 2. Ascites ---serum albumin低
- 3. **Hepatic encephalopathy** →
- Hepatic odor
- **Flapping tremor**
- NH3 increased
- EEG change: triphasic wave.

31.炎症指標, 不同疾病變化不同 (timing)

Inflammatory parameters

WBC

DC─ : PMN : Shift to left

Neutrophilia(>5,000)

CRP

ESR

LDH

……

①normal range

②data 變化,判斷

Progression

Improvement

32. 表示severe inflammation and tissue reaction

- WBC>15,000甚至>20,000
- Neutrophils >85% or >10,000
- **CRP>8 甚至>12**
- severe Infection-
- **Sepsis--Blood cultures**
- Abscess: liver or retroperitoneal
- - CT and abd sono--aspiration
- SBE->infectious endocarditis
- PE and cardiac echo.

33, CRP>20

- 危險值,
  - Tissue reaction→ necrosis
  - Intestinal perforation (ileus)
  - UC- severe, associated with active bleeding
  - Toxic megacolon in UC, CMV, amebic, PMC
  - sepsis, critical

- Interpretation of data :

  0.8—3.0 --------
  mild

  3.0-8.0 ----------
  moderate

  8 --20 severe

  More than 20 ---- very high , cautious.

34. HCC: 甲型胎兒蛋白

AFP：代表肝細胞之再生及惡化

less than 20…仍有30%HCC，AFP不增加

20-200---20 % 是HCC

200-400　90%是HCC

>400 …　99%以上是HCC

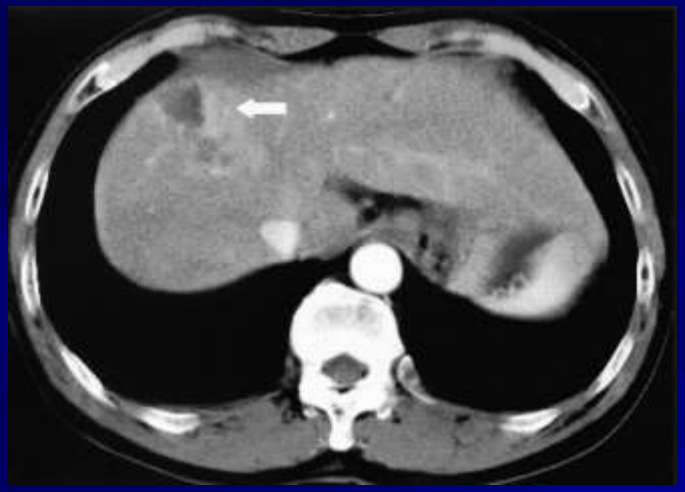
>5,000 …　99.99 %以上是HCC

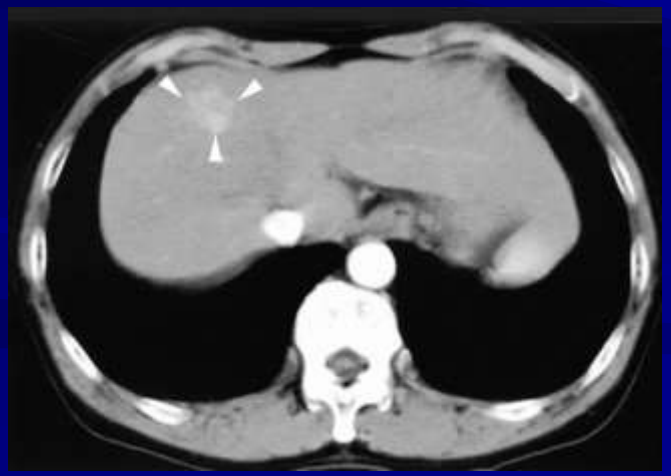
>10,000　100%是HCC

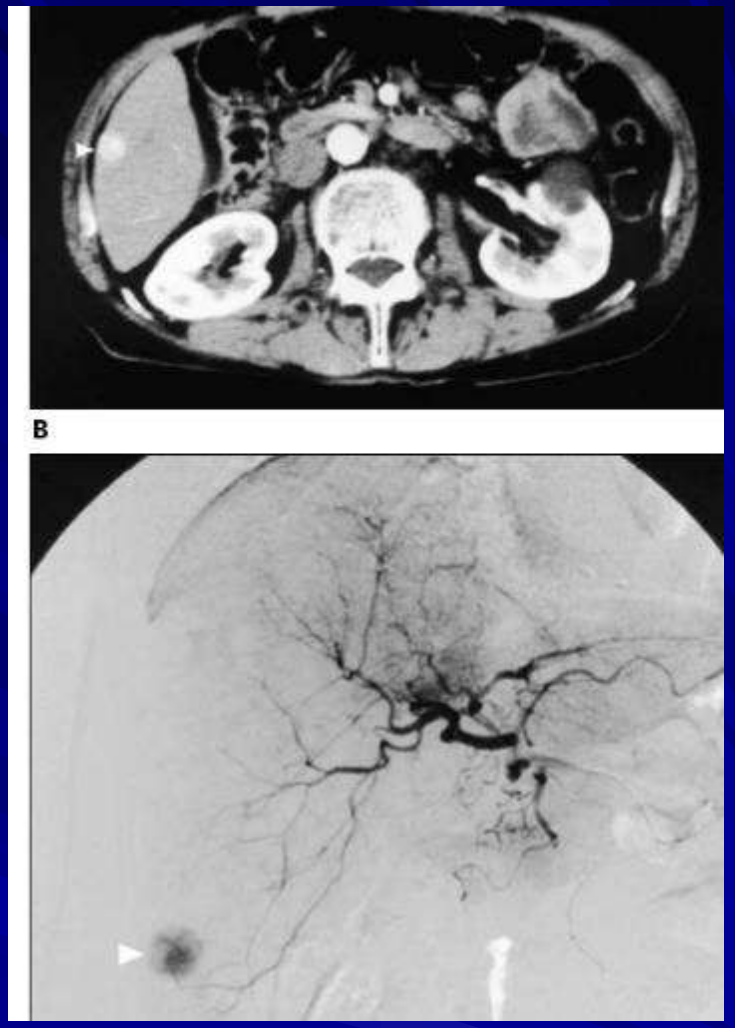
Ex. AFP>400 …　99%以上是HCC

- No evidence of severe liver necrosis within 2 months.
- Careful investigation should be done.
- Notice minor changes in abdominal CT and angiography

35. 有機會找到Small HCC, by angio







Small Hepatocellular Carcinoma Therapeutic Effectiveness of Percutaneous Radio Frequency Ablation Therapy With a LeVeen Needle Electrode
Kazuhito Shirato, MD, et al J Ultrasound Med 21:67–76, 2002

36. Normal AFP HCC-在發展中

- **Prognosis evaluation in alpha-fetoprotein negative hepatocellular carcinoma after hepatectomy: comparison of five staging systems.** Zhang XF[1] et al)西安交大丿:Eur J Surg Oncol. 2010 Aug;36(8):718-24.
- The data of 306 in total and 98 AFP negative patients
- AFP negative patients tended to have **intact tumor capsule and earlier staged tumor** by TNM, CLIP and BCLC. The independent risk factors worsening overall survival of AFP negative patients were absence of tumor capsule, Child-Pugh classification B, hepatitis B surface antigen positive and BCLC stage B-C.
- Normal AFP level implies earlier staged tumors. BCLC has the strongest potential in prognosis evaluation in AFP negative patients.

神經突生長促進因子2（NEGF2）Midkine

Midkine Increases Diagnostic Yield in AFP Negative and NASH-Related Hepatocellular Carcinoma.

- Roslyn Vongsuvanh et al (Sudney Univ. Australia) PLOS, May 24, 2016.
- **serum midkine (MDK**), dickkopf-1 (DKK1), osteopontin (OPN) and AFP for HCC diagnosis in 86 HCC patients matched to 86 cirrhotics, 86 with chronic liver disease (CLD) and 86 healthy controls (HC).
- More than half of HCC patients had normal AFP. In this AFP-negative HCC cohort, 59.18% (n = 29/49) had elevated MDK, applying the optimal cut-off of 0.44 ng/ml.
- Using AFP ≥ 20 IU/ml or MDK ≥ 0.44 ng/ml, a significantly greater number (76.7%; n = 66/86) of HCC cases were detected
- **Conclusion:** AFP and MDK have a complementary role in HCC detection. MDK increases the diagnostic yield in AFP-negative

New Biomarkers for Hepatocellular Carcinoma

Roongruedee Chaiteerakij, MD, Benyam D. Addissie, MD,
Lewis R. Roberts, MD, PhD
Mayo Clinic
Rochester, MN

New Treatments in Liver Disease

American Association for the Study of Liver Diseases

World J Gastroenterol. 2015 Oct 7; 21(37): 10573–10583.
Published online 2015 Oct 7. doi: 10.3748/wjg.v21.i37.10573
PMCID: PMC458807
PMID: 2645701

Biomarkers for the early diagnosis of hepatocellular carcinoma

Nobuhiro Tsuchiya, Yu Sawada, Itaru Endo, Keigo Saito, Yasushi Uemura, and Tetsuya Nakatsura

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Nobuhiro Tsuchiya, Keigo Saito, Yasushi Uemura, Tetsuya Nakatsura, Division of Cancer Immunotherapy, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center, Kashiwa 277-8577, Japan

Advances in genomics and proteomics platforms and biomarkers assay techniques over the last decade have resulted in the identification of numerous novel biomarkers and have improved the diagnosis of HCC. The most promising biomarkers, such as glypican-3, osteopontin, Golgi protein-73 and nucleic acids including microRNAs, are most likely to become clinically validated in the near future.

HCC biomarkers are used for predicting risk for HCC development, screening and surveillance, diagnosis, stratifying patients for targeted therapy, monitoring treatment response, and predicting HCC recurrence and patient survival. A number of SNPs have been identified as new biomarkers for HCC risk prediction. For HCC diagnosis, the serum AFP remains a useful biomarker, with a higher sensitivity than AFP-L3 and DCP. The combination of AFP with AFP-L3 or DCP may be better than using AFP alone as a biomarker for HCC diagnosis. Recent findings suggest that the combination of AFP with other variables, such as ALT, or patient and tumor characteristics (e.g. the MESIAH score), improves performance of AFP for early HCC detection and

Review > Clin Mol Hepatol. 2025 Feb;31(Suppl):S228-S254. doi: 10.3350/cmh.2024.0824.
Epub 2024 Dec 26.

Hepatocellular carcinoma: updates on epidemiology, surveillance, diagnosis and treatment

Soo Young Hwang [1], Pojsakorn Danpanichkul [2], Vatche Agopian [3], Neil Mehta [4], Neehar D Parikh [5], Ghassan K Abou-Alfa [6 7 8], Amit G Singal [9], Ju Dong Yang [10]

Affiliations – collapse

Affiliations

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肝細胞癌（HCC）是全球的主要負擔，是癌症相關死亡的第三大原因。由於 HBV 的普遍疫苗接種和對 HBV 和 HCV 的有效抗病毒治療，慢性乙型肝炎病毒（HBV）或 C 病毒（HCV）感染引起的 HCC 有所減少，但與代謝功能障礙相關的脂肪性肝病和酒精相關肝病相關的 HCC 正在增加。**一年兩次的肝臟超聲檢查和血清α-胎蛋白是高危患者（例如肝硬化、慢性 HBV）早期 HCC 檢測的主要監測工具**。正在研究其他監測工具，例如基於血液的生物標誌物面板和簡化的磁共振成像（MRI）。多相計算機體層成像或 MRI 是 HCC 診斷的標準，但應考慮組織學確認，尤其是當橫斷面影像學檢查發現不確定時。分期和治療決策很複雜，應在多學科環境中做出，包括腫瘤負荷、肝功能障礙程度、患者體能狀態、現有專業知識和患者意願。早期 HCC 最好採用根治性方案進行治療，例如切除術、消融術或移植術。對於中期疾病，主要推薦局部區域治療，但對於肝內腫瘤負荷較大的患者，可能首選全身性治療。在疾病晚期，基於免疫檢查點抑製劑的治療是首選的治療方案。

- 儘管每種生物標誌物在單獨使用時對早期階段的敏感性不足，但包括多個生物標誌物的生物標誌物面板似乎具有更高的準確性。最初的肝細胞癌早期檢測篩查（hepatocellular carcinoma early detection screening， HES）評分結合AFP與年齡、ALT和血小板計數相結合，在檢測早期HCC方面優於單獨使用AFP，並且提出了包括AFP-L3和des-γ-羧基凝血酶原的最新版本的**HES V2.0，性能優異[112,113]。GALAD（性別、年齡、AFP-L3、AFP、des-γ-羧基凝血酶原）模型結合了三種生物標誌物**，最近在一項國家 3 期生物標誌物研究中進行了評估，證明準確性有所提高：GALAD 在 6、12 和 24 個月內具有最高的真陽性率（所有 HCC 為 63.6%、73.8% 和 71.4%，早期 HCC 為 53.8%、63.3% 和 61.8%），

- 1. hepatocellular carcinoma early detection screening (**HES**) score combining AFP with age, ALT, and platelet count has shown to be superior to AFP alone for detection of early HCC.
- 2.Gerad Model: he GALAD (gender, age, AFP-L3, AFP, des-gamma-carboxy prothrombin) model combined the three biomarkers and was recently evaluated
- 3. Liquid biopsy : a six-marker methylated DNA marker panel (*HOXA1, EMX1, AK055957, ECE1, PFKP, CLEC11A*) yielded an area under the curve (AUC) of 0.96 with a sensitivity of 95% and specificity of 92% [119]
- 4. Abbreviated MRI is undergoing prospective validation in large trials in the US, France, and South Korea (86% sensitivity and 94% specificity)

AMRI+US

- Nahon P, Ronot M, Sutter O, Natella PA, Baloul S, DurandZaleski I, et al. Study protocol for FASTRAK: a randomised controlled trial evaluating the cost impact and effectiveness of FAST-MRI for HCC suRveillance in pAtients with high risK of liver cancer. BMJ Open. 2024;14:e083701. doi: 10.1136/bmjopen-2023-083701.

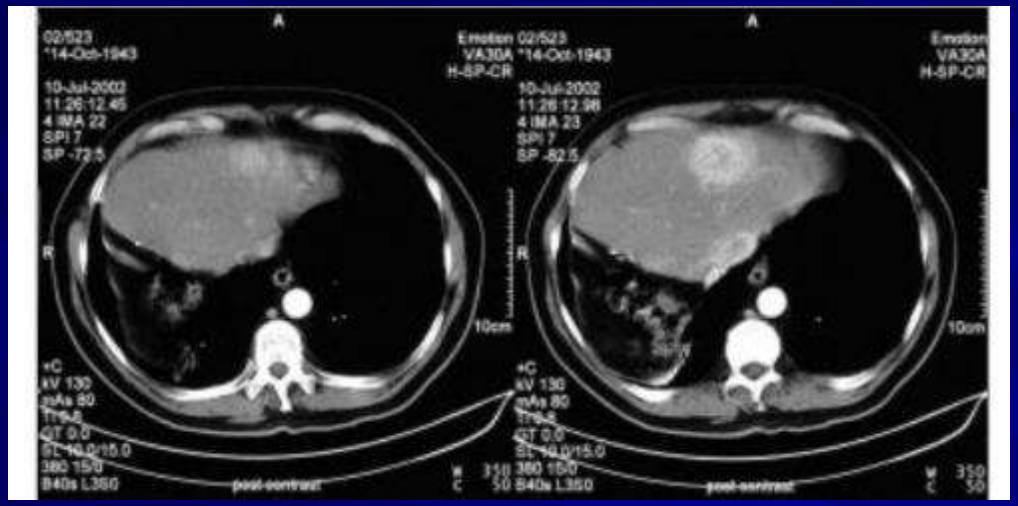
簡化肝臟 MRI （AMRI） 的敏感性超過 80%，但其使用受到成本和可用性的阻礙。我們的假設是，將AMRI用作HCC高危患者（每年 >3%）的篩查檢查可以提高早期可進行根治性治療的腫瘤患者的發生率，並證明其在該人群中的成本效益。

方法與分析： FASTRAK 試驗是一項多中心、隨機對照試驗，有兩個平行組，旨在提高優勢，並在 HCC 高危患者（每年 HCC 發病率 >3%）中進行。隨機化將以個人為基礎進行，採用集中方法並按中心分層。納入試驗后，每位患者將被隨機分配到實驗組（半年一次US和AMRI）或對照組（僅半年一次US）。主要目的是評估在兩組中檢測到 BCLC 0 HCC 的成本/質量調整生命年和成本/患者。在 36 個月的時間內，將在 37 個三級法國中心招募總共 944 名患者，並將在 36 個月內接受隨訪。

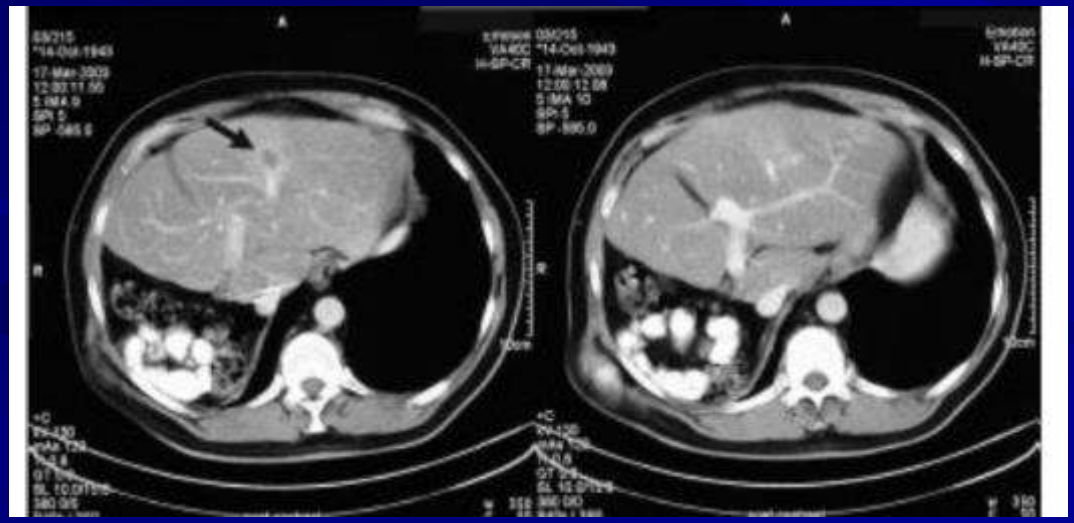
道德與傳播： FASTRAK 試驗於 2022 年 4 月 4 日獲得倫理批准。結果將通過在同行評審期刊上發表以及在國際會議上展示來傳播。

試驗註冊號： 臨床試驗編號 （ClinicaTrials.gov） NCT05095714。

37. Check Imaging in Metastatic cancer



CT scans taken in the portal venous phase show a hypervascular metastatic deposit from a renal cell carcinoma. The patient had a previous right hepatectomy for an earlier renal cell solitary metastatic deposition.



CT scan in the same patient as in the previous image following immunotherapy. Note the considerable reduction in the size of the liver lesion.

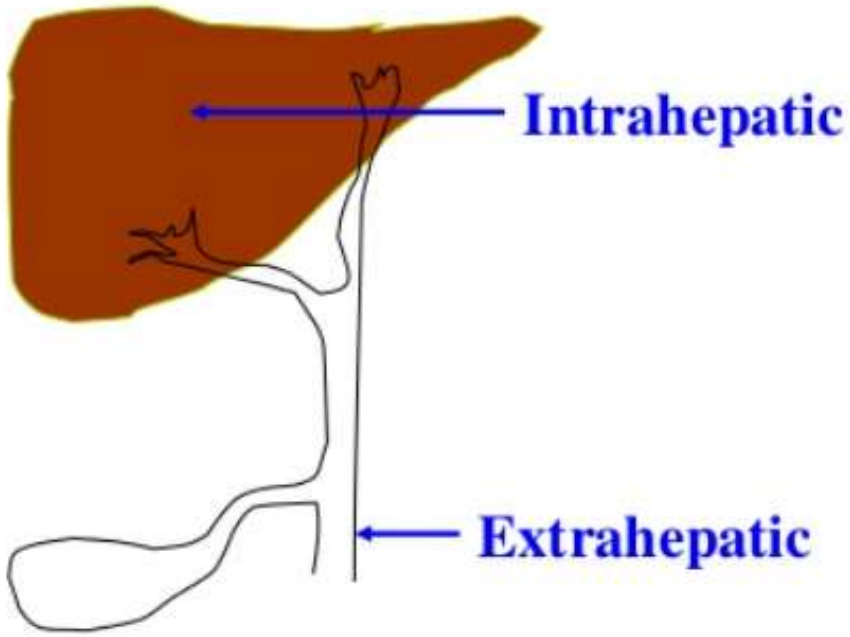
38. Cholestasis

- **Cholestasis** is a condition where bile cannot flow from the liver to the duodenum. The two basic distinctions are an obstructive type of cholestasis where there is a mechanical blockage in the duct system that can occur from a gallstone or malignancy, and metabolic types of cholestasis which are disturbances in bile formation that can occur because of genetic defects or acquired as a side effect of many medications.

Cholestasis (Greek-bile stoppage)

Reduction or absence of bile flow into duodenum

很多不同的原因

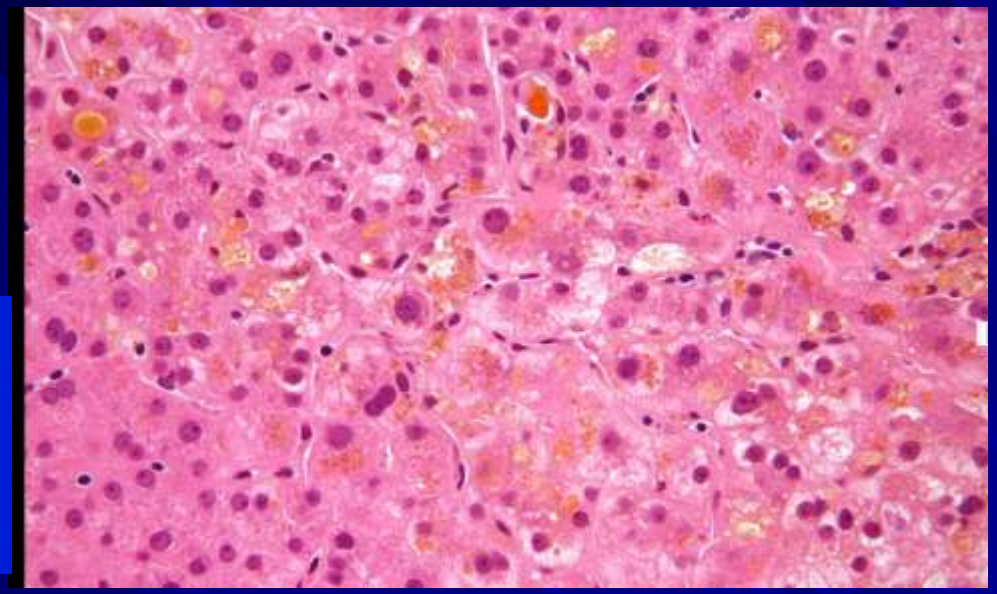


- Impairment of bile secretion at the level of bile ductules (ductular cholestasis)
- Functional defect in bile formation at hepatocyte level (hepatocellular chlestasis)

Chronic if > 6mo duration
Etiology: differs across ages
Alkaline phosphatase >1.5ULN, GGT> 3ULN*

Cholestasis

the individual hepatocytes will have a brownish-green stippled appearance within the cytoplasm, representing bile that cannot get out of the cell. Canalicular bile plugs between individual hepatocytes

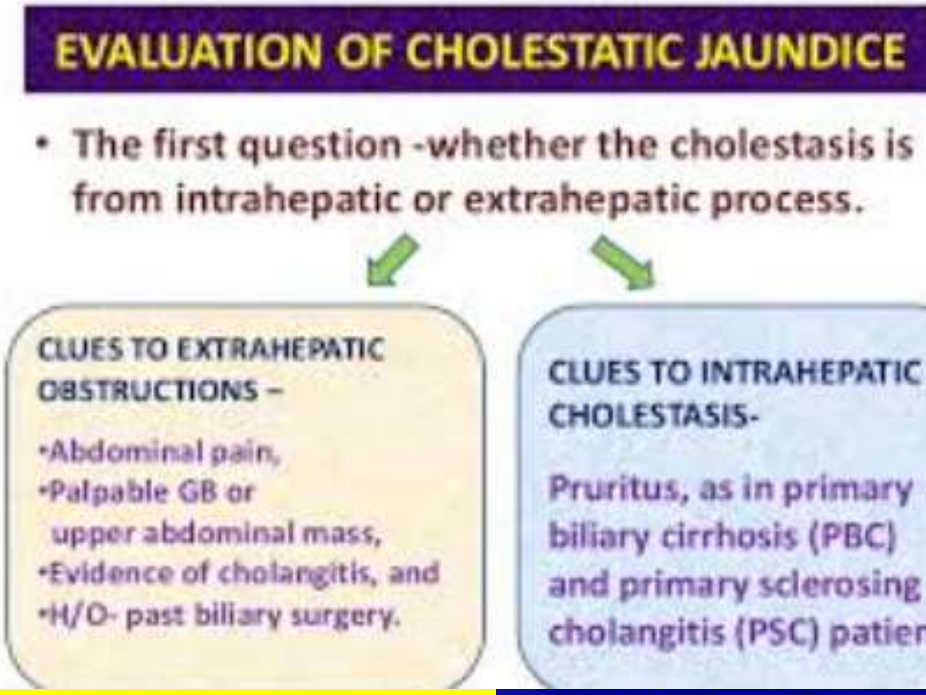


- Cholestasis can be suspected when there is an **elevation of both 5'-nucleotidase and ALP enzymes**. With a few exceptions, the optimal test for cholestasis would be elevations of serum bile acid levels. However, this is not normally available in most clinical settings. **The gamma-glutamyl transferase (GGT) enzyme was previously thought to be helpful in confirming a hepatic source of ALP**; however, GGT elevations are markedly sensitive and lack the necessary specificity to be a useful confirmatory test for ALP. Normally GGT and ALP are anchored to membranes of hepatocytes and are released in small amounts in hepatocellular damage.

Cholestasis, intrahepatic

Intrahepatic cholestasis occurs inside the liver. It can be caused by:

- Alcoholic liver disease
- Amyloidosis
- Bacterial abscess in the liver
- Being fed exclusively through a vein (IV)
- Lymphoma
- Pregnancy
- Primary biliary cirrhosis
- Primary or metastatic liver cancer
- Primary sclerosing cholangitis
- Sarcoidosis
- Serious infections that have spread through the bloodstream (sepsis)
- Tuberculosis



1.Itching→intrahepatic
2. CBD dilatation-
→extrahepatic.

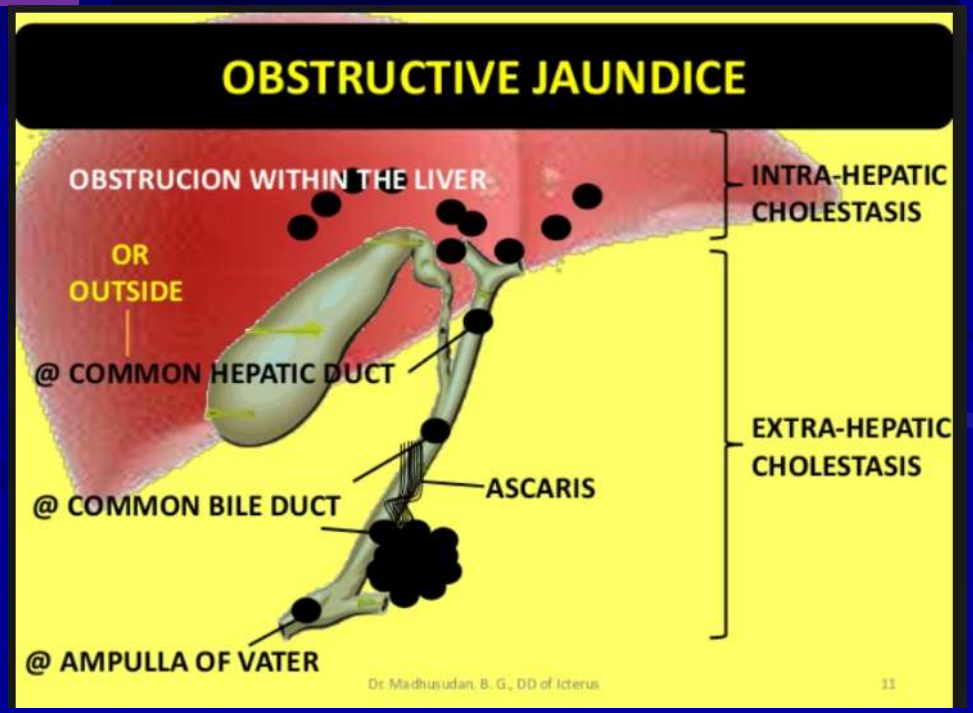
intrahepatic cholestasis of pregnancy

- Intrahepatic cholestasis of pregnancy is a liver disorder that occurs in pregnant women. Cholestasis is a condition that impairs the release of a digestive fluid called bile from liver cells. As a result, bile builds up in the liver, impairing liver function. Because the problems with bile release occur within the liver (intrahepatic), the condition is described as **intrahepatic cholestasis**. Intrahepatic cholestasis of pregnancy usually becomes apparent in the third trimester of pregnancy. **Bile flow returns to normal after delivery** of the baby, and the signs and symptoms of the condition disappear. However, they can return during later pregnancies. This condition causes severe itchiness (pruritus) in the expectant mother. The itchiness usually begins on the palms of the hands and the soles of the feet and then spreads to other parts of the body.

Obstructive JAUNDICE

- Gall stone with obstructive jaundice due to impacted stone at CBD
- Obstructive jaundice due to pancreatic head cancer

US
Abdominal CT
ERCP
MRCP
Tests.bilirubin/GGT
Tumor markers
PTC



39. Within 72 hours
找出阻塞性黃疸的原因並處理之,達到減黃之目的

- Dx of obstructive jaundice
- Evaluation
- Check site of obstruction
- Check causes , **benign or malignant**
- Relief of obstruction at least reduction of jaundice.(biliary stents, PTCD, or surgery)

40. CEA值可供手術─切除與否之參考

- **注意不同方法之CEA值不可比較**
- **不同之lab 之檢查結果可供參考，不宜比較其大小**
- CEA值可供手術─切除與否之參考

CEA in Colorectal cancer 大腸癌 40-44 % (+)

<5…(正常值) …100%可切

5~10…(稍高) … 90%仍可開刀

10-20…(相當高) …50%可開

>20…(很高) … 1/7(14-15%)可開

HB markers

Test	Result	Interpretation
HBsAg anti-HBc anti-HBs	negative negative negative	Susceptible (vaccinate)
HBsAg anti-HBc anti-HBs	negative positive positive	Infected but resolved. Resolved HBV infection
HBsAg anti-HBc anti-HBs	negative negative positive	Vaccinated **Anti HBc (-)**
HBsAg anti-HBc anti-HBs	positive positive negative	Active HBV infection (usually chronic) *If anti-HBc IgM present, may represent acute infection.
HBsAg HBcAb HBsAb	negative positive negative	Various possibilities: distant resolved infection (most common) recovering from acute infection false positive occult hepatitis B

一定找出檢驗異常的原因

- Severe anemia
- Hyperbilirubinemia
- Liver cell necrosis—
  SGOY and SGPT > 300
- Abnormal alkaline phosphatase and GGT
- =bone growing—alkaline phosphatase
- =biliary obstruction and cholestasis-both
- Alcoholic ---GGT
- Neoplastic—both GGT and ALP

What are the causes of liver cell necrosis?

- Hepatitis
- Heart failure
- Drugs
- Fatty liver
- Alcohol and
- or other liver toxins
- Marijuana (cannabis) smoking
- leptospirosis
- ---

recognised causes of acute liver cell necrosis:

The following are recognised causes of acute liver cell necrosis:
(i) paracetamol overdose
(ii) severe heart failure
(iii) human papilloma virus
(iv) leptospirosis
(v) cannabis smoking

Sonia, 2008.

原因很多, 好好詢問病史可能可以了解, 找出原因

Physical check up健檢

- 早期發現問題:
- Abnormal ? 紅字
- -→是 acute change 還是 chronic
- --->調整生活方式/治療之效果
- **Data 之分析會比較嚴格,以求改善**
- **改變生活習慣:運動**
- Diet. Change
- 要Follow up.
- 注意所訂之 normal range.

Normal ranges是人設定的 電腦處理是死的

- Serum cholesterol : up to 200 (normal range)
- **201: abnormal**
- Lab cv ratio <5 % good quality
- 200X0.05=10
- 210=190 ---故 201 仍是正常

- *the **coefficient of variation (CV)**, also known as **relative standard deviation (RSD)***

摘要(2025.04.18)

- 1. 一般常用的檢驗項目要熟悉 Normal ranges, clinical significance.思考不正常所代表的意義.與主要疾病有無關連.
- 2. 很多檢驗數據因Lab. 品質不良, Lab error大,會影響判斷
- 3. Lab data 可作疾病變動的指標(信號), 必須參考症狀及徵象之變動.
- 4. **一定要紀錄在病歷之上, 而且至少要在一週內Follow up.**(主要變化時要 QD or Q2D)