Original Article

Prevalence of Cirrhosis in Patients with Thrombocytopenia Who Receive Bone Marrow Biopsy

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ABSTRACT

Background/Aim: Thrombocytopenia is a common finding in patients with cirrhosis and may lead to unnecessary referral for bone marrow (BM) biopsy. To date, the prevalence of cirrhosis in patients with thrombocytopenia who receive BM biopsy is largely unknown. **Materials and Methods:** Between fiscal years 2006-2010, 744 patients (≥18 years) who underwent BM biopsies for thrombocytopenia at our hospital were identified retrospectively. 541 patients were excluded who had hematologic malignancies and received chemotherapy. Remaining 203 patients with predominant isolated thrombocytopenia were included in the study. **Results:** Of 203 patients, 136 (67%) had a normal and 67 (33%) had an abnormal BM examination. Prevalence of cirrhosis in the study population was 35% (95% CI: 28.4-41.9). 51% patients with normal BM were found to have cirrhosis compared to 3% of patients with abnormal BM exam ($P < 0.0001$). Common causes of cirrhosis were nonalcoholic steatohepatitis (NASH) (47%), followed by alcohol and Hepatitis C virus infection. Idiopathic thrombocytopenia and myelodysplastic syndrome were most frequent causes of thrombocytopenia in patients without cirrhosis. Patients with NASH had higher body mass index (BMI) (33.4 vs. 25.8, $P < 0.001$) and lower MELD scores (11.1 vs. 16, $P = 0.028$) when compared to non-NASH patients with cirrhosis. **Conclusion:** Approximately, one third (35%) of patients with cirrhosis induced thrombocytopenia may undergo unwarranted BM biopsies. Clinical diagnosis of cirrhosis is still a challenge for many physicians, particularly with underlying NASH. We propose cirrhosis to be the prime cause of isolated thrombocytopenia.

Key Words: Bone marrow biopsy, chronic hepatitis C, chronic liver disease, cirrhosis, non--alcoholic steatohepatitis (NASH), thrombocytopenia

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Thrombocytopenia, defined as a platelet count of less than 150,000 cells/μL is a common manifestation occurring in approximately 64-76% of patients with portal hypertension and underlying cirrhosis.[1,2] Factors contributing to the development of thrombocytopenia in cirrhosis include splenic sequestration of platelets, bone marrow suppression, interferon based therapies, and reduced level or activity of thrombopoietin (TPO).[3-6] TPO is predominantly produced in the liver, and thrombocytopenia may develop when TPO is increasingly degraded by platelets sequestered in the congested spleen.[7] In patients with hepatitis C related liver disease, autoantibodies against platelet surface antigens can promote platelet sequestration and destruction by cells of the reticulo-endothelial system.[8]

Cirrhosis is a histological diagnosis; however in patients with chronic liver disease (CLD), presence of various clinical features[9] can suggest cirrhosis, and liver biopsy is mostly redundant and unsafe.[10,11] In clinical practice, history of predisposing factors, presence of stigmata of CLD, palpable left lobe or small liver span, splenomegaly, signs of liver decompensation, findings on abdominal imaging studies,[12,13] laboratory data,[14,15] and upper endoscopic findings[16,17] usually provide major clues for underlying cirrhosis. One study demonstrated that cirrhosis can be correctly diagnosed in 82-88% of patients with CLD by simply using a few ultrasonographic signs. Nonetheless, the

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diagnostic accuracy of ultrasound is decreased by anatomical limitations of this technique.[18] Another study determined the utility of a panel of serum fibrosis markers along with routine laboratory tests in estimating the likelihood of histological cirrhosis in a cohort of prior non-responders with chronic hepatitis C.[19] In recent years, noninvasive tests have shown their ability to identify significant fibrosis and cirrhosis.[20,21]

Bone marrow biopsy is frequently done in clinical practice to evaluate thrombocytopenia. It is an invasive procedure that carries risks of pain, bleeding and infection.[22,23] Potentially fatal cardiovascular complications have been noted with sternal aspiration.[24] Two deaths attributed to laceration of blood vessels have been reported in the literature.[25,26] Patients with cirrhosis are particularly at a greater risk for hemorrhage with bone marrow biopsy.[27]

To date, the prevalence of cirrhosis in patients with thrombocytopenia who undergo bone marrow is unknown. Routinely, we encounter several patients referred to us by hematologists for the evaluation of cirrhosis after an extensive negative work-up for thrombocytopenia. The aim of this study was to precisely evaluate such prevalence.

MATERIALS AND METHODS

Patient selection

Retrospectively, 744 patients with age ≥18 years who underwent bone marrow biopsies/aspirations between the fiscal years 2006 and 2010 at Community Regional Medical Center, an urban tertiary referral teaching hospital and Cancer Care Associates, Fresno, California for thrombocytopenia were initially identified by using electronic medical records and appropriate ICD codes. Among them, patients with hematologic malignancies, and those who received chemotherapy during the past 3 months were excluded. The remaining 203 patients were included in the study. This study was approved by the University of California, San Francisco, Fresno Medical Education Program (UCSF Fresno MEP) institutional review board.

Diagnosis of cirrhosis

Cirrhosis was diagnosed clinically in majority of cases except for few patients who have had liver biopsies in the past. Combinations of various pertinent clinical findings such as ascites, splenomegaly, endoscopic evidence of esophageal varices and/or radiologic evidence of cirrhosis were used to establish the clinical diagnosis of cirrhosis.[9,12-17] Non-alcoholic steatohepatitis (NASH) induced cirrhosis was diagnosed after exclusion of other causes of cirrhosis along with the presence of features of metabolic syndrome, such as body mass index (BMI>25), hypertension (HTN), diabetes mellitus (DM) and dyslipidemia.

Viral hepatitis panels, antinuclear antibody, anti-smooth muscle antibody, anti-mitochondrial antibody, coagulation parameters, ceruloplasmin, and iron studies were available for most of the patients. Also, patients' demographics and past medical, surgical and social history along with imaging studies and endoscopic findings were reviewed retrospectively. The models for end-stage liver disease (MELD) scores were calculated.

Bone marrow analysis

The primary indication for BM biopsy was isolated thrombocytopenia. All patients were evaluated for cellularity, dysplasia, malignancy, lymphocytosis, plasmacytosis, and myeloid: erythroid ratio. A diagnosis of dysplasia was made when signs of dyspoiesis in the erythroid lineage (nuclear irregularities, nuclear budding, internuclear bridging), myeloid lineage (abnormal lobation and/or granulation), and/or megakaryocytic lineage (small hypolobated forms, multinucleated forms) were present in greater than 10% of the cells within each lineage, in accordance with current World Health Organization criteria.[28,29]

Statistical analysis

The collected data was tabulated using Microsoft excel and analysis was performed using Stata, version 11.1. Continuous variables are summarized as mean ± standard deviation and, comparisons between continuous variables were analyzed using Student t test. Wilcoxon (Mann-Whitney) rank-sum test was used to calculate *P* value for continuous variables with non-Gaussian distribution and values reported as median. Categorical variables are summarized as percentage of the group total and, comparisons between groups were analyzed using Fisher exact test or Chi-square test where appropriate. A *P* value of less than 0.05 was considered to be statistically significant. Prevalence rates with 95% Confidence Interval (CI) were reported where necessary.

RESULTS

During the study period from 2006 to 2010, a total of 203 patients who underwent BM biopsy for the diagnostic evaluation of thrombocytopenia were identified (Males = 117; Females = 86) with mean age of 60.2 ± 17.4 years, range 18-93 years [Table 1]. Mean platelet count in the study population was found to be 69.9 ± 33 k/uL.

Out of 203 isolated thrombocytopenia patients, 24 (12%) had known pre-existing liver disease, while 179 (88%) had no known underlying liver disease. Among patients with pre-existing liver disease (n = 24), only one had an abnormal bone marrow biopsy positive for Coccidoidomycosis, and among those with no known underlying liver disease (n = 179), 113 (63%) had normal BM biopsy and 67 (37%) had abnormal BM biopsy results. Further analysis revealed

that 47 (about 25%) patients with no known pre-existing liver disease were found to have cirrhosis and only one patient among them had an abnormal bone marrow exam consistent with myelofibrosis [Figure 1].

Total prevalence of cirrhosis in the study population was found to be 35% (95% CI: 28.4-41.9). 51% patients with normal BM examination were found to have cirrhosis compared to 3% of patients with abnormal BM exam ($P < 0.0001$).

Based on predominant etiology of cirrhosis, study patients were categorized into NASH and non-NASH groups. Table 2 lists the comparisons between these two groups. The groups were similar with respect to sex and mean age. The mean BMI of patients with NASH was significantly higher than patients with all other etiologies of cirrhosis (33.4 ± 5.7 versus 25.8 ± 6). NASH group had higher albumin levels compared to non-NASH group ($P = 0.015$). MELD scores were relatively lower in NASH group when compared with non-NASH group (11.1 ± 7.1 versus 16 ± 8.6, $P = 0.028$). No statistically significant differences were noted across ethnicities and in other findings like platelet counts, ascites, splenomegaly, hepatomegaly, and hepatic encephalopathy. Various other relevant clinical and laboratory parameters compared between NASH and non-NASH groups are listed in Table 2.

Table 1: Baseline demographics of the study subjects

Demographics (n = 203)	Values
Age in years (mean ±SD)	60.2 ± 17.4
Gender	
Male—no. (%)	117 (57.6)
Female—no. (%)	86 (42.4)
Race/Ethnic group-no. (%)	
White	70 (34.5)
Hispanic	67 (33)
Asian	32 (15.8)
African American	19 (9.4)
Others and unknown	15 (7.4)

Bone marrow findings

Out of 203 study patients, 67 with normal bone marrow (49% of patients with normal BM or 33% of all study patients) had etiology of thrombocytopenia other than cirrhosis. Among non-cirrhotic patients, idiopathic thrombocytopenic purpura (ITP) (29 patients; 21% of normal BM) was the most common finding followed by unknown etiology (20 patients; 15% of normal BM). About 5% had the miscellaneous causes of thrombocytopenia, such as drug induced thrombocytopenia, disseminated intravascular coagulation and Mycobacterial infection. Out of all patients who had abnormal BM, only two patients had cirrhosis as described above. Most common findings in this group were myelodysplastic syndrome (MDS) followed by leukemia and myelofibrosis [Tables 3 and 4].

DISCUSSION

Thrombocytopenia is the most common and first abnormal hematologic indices to occur in patients with cirrhosis, followed by leukopenia and anemia.[2,30] Thrombocytopenia should

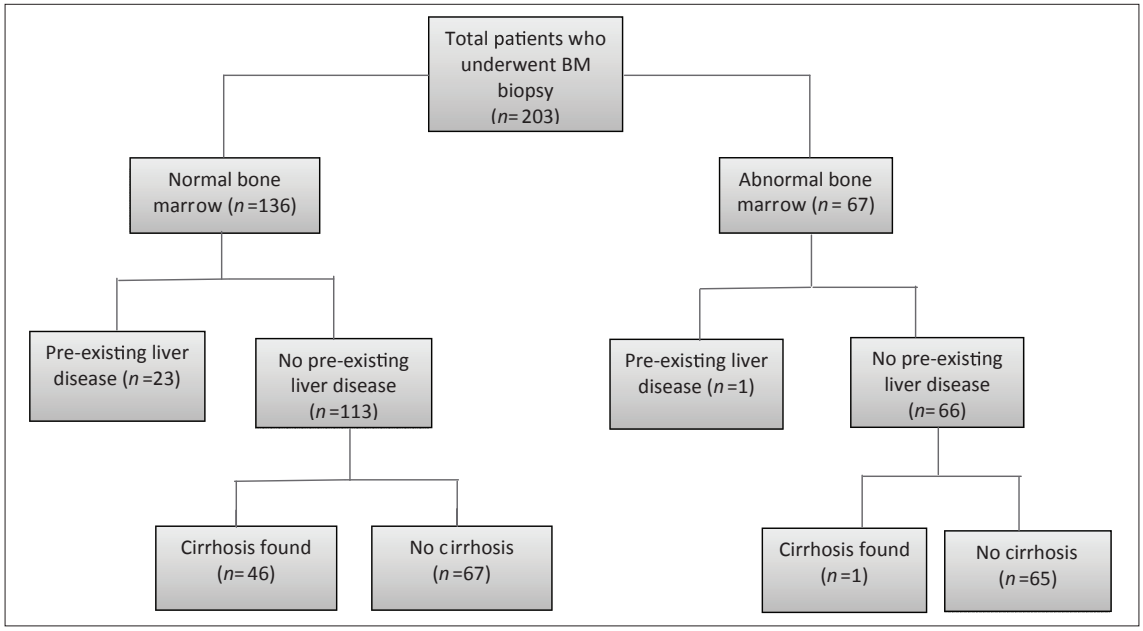

Figure 1: Schema of the study patients who underwent BM biopsy for thrombocytopenia

Table 2: Comparison of baseline characteristics of NASH and Non-NASH subjects

Characteristics	NASH (*n* = 33)	Non-NASH (*n* = 38)	*P* value*
Demographics			0.169
Age—years (mean ± SD)	63.6 ± 12	59.5 ± 12.7	
Gender			0.638
Male—no. (%)	17 (51)	22 (58)	
Female—no. (%)	16 (48.5)	16 (42)	
Race/Ethnic group—no. (%)			0.609
White	12 (36.4)	13 (34)	
Hispanic	10 (29)	11 (30)	
Asian	7 (21.2)	4 (10.5)	
African American or Black	2 (6.1)	7 (18.4)	
Others and unknown	2 (6.1)	3 (8)	
BMI—kg/m²(mean ± SD)*Labs*	33.4 ± 5.7	25.8 ± 6	<0.0001
Platelets—(mean ± SD)K/ul	77.2 ± 28.3	65.5 ± 27.8	0.084
WBC counts—median(range) K/ul	4.2 (1.4-11)	4.3 (1.4-36)	0.665
Hemoglobin—(mean ± SD) (g/dl)	12 ± 2.3	10 ± 2.1	0.003
Liver function tests			
AST—median(range) U/L	30.5(12-523)	41.5 (15-377)	0.031
ALT—median(range) U/L	29 (12-350)	43.5 (9-985)	0.037
AlkPhos—(mean ± SD)U/L	103.5 ± 54.8	172 ± 136	0.010
Bilirubin—median(range) mg/dl	1.2(0.2-13.5)	1.3 (0.3-15.9)	0.409
Albumin—(mean ± SD)g/dl	3.5 ± 0.9	3 ± 0.8	0.015
Creatinine—median(range) mg/dl	1(0.4-11)	1.3 (0.4-7.8)	0.039
INR—(mean ± SD)	1.3 ± 0.7	1.7 ± 1.2	0.240
LDL—median(range) mg/dl	61 (44-279)	77 (36-286)	0.731
Triglycerides—median(range) mg/dl	122 (40-207)	100.5 (42-269)	0.674
HbA1c—(mean ± SD)	7.3 ± 1.7	6.2 ± 1.1	0.105
Glucose—median (range) mg/dl	154 (86-364)	135 (81-392)	0.079
Ascites—no. (%)	8 (25.8)	15 (39.5)	0.173
US/CT imaging available—no. (%)	30 (90.9)	32 (84.2)	0.316
Splenomegaly—no. (%)	16 (53.3)	17 (53)	0.954
Hepatomegaly—no. (%)	7 (23.3)	13 (42)	0.101
Fatty liver—no. (%)	8 (26.7)	4 (12.9)	0.152
Cirrhotic liver—no. (%)	14 (46.7)	15 (46.9)	0.594
Hepatic Encephalopathy—no. (%)	5 (15.6)	11 (30.6)	0.122
No preexisting liver disease—no. (%)	29 (87.9)	18 (47.4)	0.000
Hypertension—no. (%)	23 (71.9)	20 (52.6)	0.080
Diabetes Mellitus—no. (%)	20 (62.5)	12 (32.4)	0.012
Dyslipidemia—no. (%)	14 (46.7)	10 (27)	0.079
MELD score—(mean ± SD)	11.1 ± 7.1	16 ± 8.6	0.028

**P* value calculated using Fisher's exact test for categorical variables and student's *t*-test for continuous variables. Wilcoxon (Mann-Whitney) rank-sum test used to calculate *P* value for variables in non-Gaussian distribution and values reported as median. *P* value < 0.05 is considered statistically significant. SD: Standard deviation , NASH: Non-alcoholic steatohepatitis, BMI: Body mass index, WBC: White blood cell count, AST: Aspartate aminotrasferase, ALT: Alanine aminotransferase, INR: International normalized ratio, LDL: Low density lipoprotein, US/CT: Ultrasound/computed tomography, MELD: Model for end-stage liver disease

therefore deserve crucial respect while evaluating patients with chronic liver disease. Severe thrombocytopenia (platelet count <50,000) is rare in cirrhosis but moderate thrombocytopenia has been found to be the most common presentation in patients with cirrhosis related hematological abnormality.[5,17] Platelet count of <88,000 is found to be associated with the presence of esophagogastric varices.[31] Mean platelet count in our total study population was 69.9 ± 33 k/uL, while it was 70.1 ± 28.4 k/uL in study patients with cirrhosis.

Due to its close association with metabolic syndrome, the liver related mortality has recently been shown to increase 10 to 20 fold, and cirrhosis is presently considered an independent cause of death, ranking third among the most frequent causes after cardiovascular disease and neoplasia.[32-35] The diagnosis of cirrhosis can sometimes be a challenge for primary care physicians. Liver biopsy which has traditionally been used to confirm cirrhosis is now rarely needed for this purpose.[10,11] As mentioned earlier, careful

Table 3: Etiology of thrombocytopenia in patients with abnormal BM findings (*n* = 67)

Etiology	Number (%)
Myelodysplastic syndrome	19 (28.4)
Leukemia	13 (19.4)
Myelofibrosis and hypocellular Marrow	10 (15)
Lymphoma	07 (10.5)
Infections	07 (10.5)
Multiple myeloma	04 (6)
Various	07 (10.5)

BM: Bone marrow

Table 4: Etiology of Cirrhosis in the study population (*n* = 71)

Etiology	Number (%)
Non-alcoholic steatohepatitis (NASH)	33 (46.5)
Alcohol	10 (14.1)
Hepatitis C	09 (12.7)
Hepatitis C and Alcohol	11 (15.5)
Hepatitis B and C	02 (2.8)
Hepatitis B	01 (1.4)
Unknown	05 (7)

history and physical examination combined with certain routine laboratory tests, imaging and endoscopic findings can usually provide important clues as to the presence of cirrhosis and may suggest an etiology.[2,9,14-18]

Although hepatitis C is considered a leading cause of cirrhosis in the United States, the prevalence of nonalcoholic fatty liver disease (NAFLD) and NASH is now increasing, and it was estimated to be 17-33% for NAFLD and 5.7-16.5% for NASH.[36] Our study clearly demonstrates that among patients with cirrhosis, NASH (47%) followed by a combination of alcohol plus HCV (16%), and alcohol alone (14%) were the most common causes of cirrhosis in patients who were referred to hematologists and underwent unwarranted bone marrow biopsy [Table 4]. This alludes to the fact that NASH is perhaps the most common cause that is likely to be missed by primary physicians due to the absence of easily noticeable etiologies of chronic liver disease.

We admit the fact that the diagnosis of NASH was based on non-invasive clinical criteria; nevertheless, the presence of higher BMI and increased prevalence of diabetes mellitus in the absence of other etiologies supported this diagnosis. In addition, there was an increased trend noted for hypertension and dyslipidemia in these subjects, though not statistically significant. Interestingly, patients with NASH were noted to have lower MELD scores, higher hemoglobin, and increased albumin as compared to non-NASH group Table 2; thus indicating an early detection and evaluation of thrombocytopenia in this particular population.

The study demonstrated that about half of the patients (51%) with normal BM had cirrhosis. In patients without cirrhosis, about 49% revealed abnormal BM results. In our study, only 2 out of 71 cirrhosis patients who underwent BM biopsy had abnormal results, indicating that the majority (97%) of patients with cirrhosis had absolutely normal BM biopsies. Out of those 71 patients, 24 had pre-existing liver disease and 47 were later found to have cirrhosis with no known pre-existing liver disease [Figure 1]. The 2 abnormal BM biopsy results among cirrhosis patients were attributed to Coccidoidomycosis and myelofibrosis respectively. These results highlight the importance of evaluating patients with thrombocytopenia for the presence of cirrhosis that would help avert unnecessary bone marrow biopsy.

Our study underscores the significance of clinical diagnosis of cirrhosis, particularly of NASH that can be challenging for both primary care physicians and various other specialists. The work up described in literature is perhaps misleading and fails to emphasize cirrhosis as an important cause of thrombocytopenia. Similarly, there are currently no appropriate guidelines for primary care physicians to triage thrombocytopenic patients to appropriate sub-specialties. The study therefore highlights the need to educate physicians on how to diagnose cirrhosis non-invasively and correlate features of metabolic syndrome with chronic liver disease. Without knowing the diagnostic significance of thrombocytopenia in cirrhosis, health care providers can easily be misguided, thus potentially affecting the overall patient care, and increasing the burden on health resources. It is important to note that patients with NASH have increased overall and liver-related mortality.[32,33]

CONCLUSION

We conclude that patients with cirrhosis and particularly, with NASH induced cirrhosis are more likely to be referred to hematologist/oncologist for the evaluation of thrombocytopenia than patients with all other etiologies leading to unwarranted BM biopsies. We strongly consider this as a lack of proper awareness about NASH, and the difficulties in diagnosing NASH induced cirrhosis in the primary care setting. This also reflects inadequacy in multidisciplinary collaborative efforts for clinical care of such patients. There is presently a substantial need for education in the area of understanding of the pathophysiological mechanisms involved in NASH, its relationships to insulin resistance and the metabolic syndrome. In future, the indications for invasive procedures such as liver and bone marrow biopsies need

to be redefined particularly in the era of rampant NAFLD and growth in the development of non-invasive modalities to diagnose cirrhosis.

REFERENCES

1. Trotter JF. Coagulation abnormalities in patients who have liver disease. Clin Liver Dis 2006;10:665-78.
2. Afdhal N, McHutchison J, Brown R, Jacobson I, Manns M, Poordad F, *et al*. Thrombocytopenia associated with chronic liver disease. J Hepatol 2008;48:1000-7.
3. Aster RH. Pooling of Platelets in the spleen: Role in the pathogenesis of hyperspenic thrombocytopenia. J Clin Invest 1966;45:645-57.
4. Kutti J, Weinfeld A, Westin J. The relationship between splenic platelet pool and spleen size. Scand J Haematol 1972;9:351-4.
5. Mayer M, Herrman I, Kempgens U, Queisser W. *In vivo* labeling of platelets with 75Se-selenomethionine in patients with hepatic cirrhosis and thrombocytopenia. Thromb Haemost 1977;37:47-52.
6. Giannini E, Borro P, Botta F, Fumagalli A, Malfatti F, Podestà E, *et al*. Serum thrombopoietin levels are linked to liver function in untreated patients with hepatitis C virus-related chronic hepatitis. J Hepatol 2002;37:572-7.
7. Rios R, Sangro B, Herrero I, Quiroga J, Prieto J. The role of thrombopoietin in the thrombocytopenia of patients with liver cirrhosis. Am J Gastroenterol 2005;100:1311-6.
8. Pereira J, Accatino L, Alfaro J, Brahm J, Hidalgo P, Mezzano D. Platelet autoantibodies in patients with chronic liver disease. Am J Hematol 1995;50:173-8.
9. Cárdenas A, Ginès P. Portal hypertension. Curr Opin Gastroenterol 2009;25:195-201.
10. Sheela H, Seela S, Caldwell C, Boyer JL, Jain D. Liver biopsy: Evolving role in the new millennium. J Clin Gastroenterol 2005;39:603-10.
11. Sanai FM, Keeffe EB. Liver biopsy for histological assessment: The case against. Saudi J Gastroenterol 2010;16:124-32.
12. Harbin WP, Robert NJ, Ferrucci JT Jr. Diagnosis of cirrhosis based on regional changes in hepatic morphology: A radiological and pathological analysis. Radiology 1980;135:273-83.
13. Giorgio A, Amoroso P, Lettieri G, Fico P, de Stefano G, Finelli L, *et al*. Cirrhosis: Value of caudate to right lobe ratio in diagnosis with US. Radiology 1986;161:443-5.
14. Williams AL, Hoofnagle JH. Ratio of serum aspartate to alanine aminotransferase in chronic hepatitis. Relationship to cirrhosis. Gastroenterology 1988;95:734-9.
15. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, *et al*. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38:518-26.
16. Ahmed S, Mumtaz K, Ahmed US, Shah HA, Abid S, Hamid S, *et al*. Frequency and characteristic features of portal hypertensive gastropathy in patients with viral cirrhosis. J Coll Physicians Surg Pak 2010;20:714-8.
17. Sanyal AJ, Fontana RJ, Di Bisceglie AM, Everhart JE, Doherty MC, Everson GT, *et al*. The prevalence and risk factors associated with esophageal varices in subjects with hepatitis C and advanced fibrosis. Gastrointest Endosc 2006;64:855-64.
18. Aubé C, Oberti F, Korali N, Namour MA, Loisel D, Tanguy JY, *et al*. Ultrasonographic diagnosis of hepatic fibrosis or cirrhosis. J Hepatol 1999;30:472-8.
19. Fontana RJ, Goodman ZD, Dienstag JL, Bonkovsky HL, Naishedham D, Sterling RK, *et al*. Relationship of serum fibrosis markers with liver fibrosis stage and collagen content in patients with advanced chronic hepatitis C. Hepatology 2008;47:789-98.
20. Martínez SM, Crespo G, Navasa M, Forns X. Noninvasive assessment of liver fibrosis. Hepatalogy 2011;53:325-35.
21. Lainé F, Bendavid C, Moirand R, Tessier S, Perrin M, Guillygomarc'h A, *et al*. Prediction of liver fibrosis in patients with features of the metabolic syndrome regardless of alcohol consumption. Hepatology 2004;39:1639-46.
22. Bain BJ. Morbidity associated with bone marrow aspiration and trephine biopsy - A review of UK data for 2004. Haematologica 2006;91:1293-4.
23. Vanhelleputte P, Nijs K, Delforge M, Evers G, Vanderschueren S. Pain during bone marrow aspiration: Prevalence and prevention. J Pain Symptom Manage 2003;26:860-6.
24. van Marum RJ, te Velde L. Cardiac tamponade following sternal puncture in two patients. Neth J Med 2001;59:39-40.
25. Roth JS, Newman EC. Gluteal compartment syndrome and sciatica after bone marrow biopsy: A case report and review of the literature. Am Surg 2002;68:791-4.
26. Bain BJ. Bone marrow biopsy morbidity: Review of 2003. J Clin Pathol 2005;58:406-8.
27. Sallah S, Bobzien W. Bleeding problems in patients with liver disease. Postgrad Med 1999;106:187-95.
28. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, *et al*. WHO classification of tumours of the haematopoietic and lymphoid tissues. Vol. 5.25. Lyon: IARC; 2008. p. 478-9.
29. Rosati S, Mick R, Xu F, Stonys E, Le Beau MM, Larson R, *et al*. Refractory cytopenia with multilineage dysplasia: Further characterization of an 'unclassifiable' myelodysplastic syndrome. Leukemia 1996;10:20-6.
30. Qamar AA, Grace ND, Groszmann RJ, Garcia-Tsao G, Bosch J, Burroughs AK, Ripoll C, *et al*. Incidence, prevalence, and clinical significance of abnormal hematologic indices in compensated cirrhosis. Clin Gastroenterol Hepatol 2009;7:689-95.
31. Zaman A, Hapke R, Flora K, Rosen HR, Benner K. Factors predicting the presence of esophageal or gastric varices in patients with advanced liver disease. Am J Gastroenterol 1999;94:3292-6.
32. Targher G, Day CP, Bonora E. Risk of Cardiovascular disease in patients with nonalcoholic fatty liver disease. N Engl J Med 2010;363:1341-50.
33. Ekstedt M, Franzén LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, *et al*. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology 2006;44:865-73.
34. Ratziu V, Poynard T. Assessing the outcome of nonalcoholic steatohepatitis? It's time to get serious. Hepatology 2006;44:802-5.
35. Ong JP, Pitts A, Younossi ZM. Increased overall mortality and liver-related mortality in non-alcoholic fatty liver disease. J Hepatol 2008;49:608-12.
36. Vernon G, Baranova A, Younossi ZM. Systematic review: The epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 2011;34:274-85.

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