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Research Article

Seasonal Patterns of Acute Esophageal Variceal Bleeding in Patients with Liver Cirrhosis

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1. Abstract

1.1. Background: Seasonal variations in the incidence of esophageal variceal bleeding in patients with end stage liver disease have been explored in various studies but the results were inconsistent.

1.2.Methods: In the present retrospective analysis, consecutive patients with liver cirrhosis admitted with esophageal variceal bleeding to the Galilee medical center from 2010 until 2015 were evaluated.

1.3. Results: The study population included 156 patients, 52% men, and mean age 64±13. Esophageal variceal bleeding exhibited a seasonal variation with peak incidence in the winter (January, February and March) (p=0.02). This finding was consistent in all subgroup analyses, including male and female gender, patients with nonalcoholic fatty liver disease (NAFLD), and patients with first episode of esophageal variceal bleeding. In multiple regression analysis, Four parameters can explain this variation, the first is NAFLD as etiology of cirrhosis in which the variation was more prominent than other etiologies (P=0.05), the second is the serum GGT level, for which the mean was the lowest in the spring, the season with the lowest rate of esophageal variceal bleeding (P=0.02), the third is the temperature in northern Israel, which is lowest in the winter (P<0.001), and the fourth is the BUN to Creatinine ratio which was highest in the winter (P=0.03).

1.4. Conclusions: There is an increased risk for esophageal variceal bleeding in Israeli patients with liver cirrhosis in the winter season. An elective endoscopy shortly before the winter season beginning may be suitable.

2. Keywords: Cirrhosis; Variceal bleeding; Portal hypertension; Seasonal variation

3. Introduction

The development of portal hypertension is the pathogen etic basis of most of the frequent and fatal complications of liver cirrhosis. Complications of cirrhosis are indicative of decompensated disease, which carries a high rate of morbidity and mortality. Patients with cirrhosis should be evaluated for the presence of varices due to the high mortality rate of esophageal variceal bleeding. At initial diagnosis, about half of patients with liver cirrhosis have esophageal varices [1-4]; the proportion reaches about 90% during the course of the disease. The 1-year rate of a first variceal bleeding is 12% [5], and the 6-week mortality with each episode of bleeding is 15-20% [6]. In patients who survive the first episode of esophageal variceal bleeding, the risk of

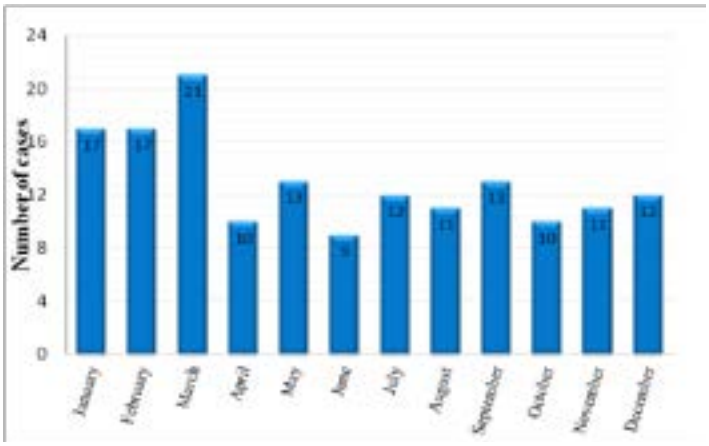

Figure 1: The distribution of all cases of variceal bleeding by month. Case were most frequent in March and least frequent in June (21 vs 9 cases, P=0.02). January, february and March are winter months, April, May and june are spring months.

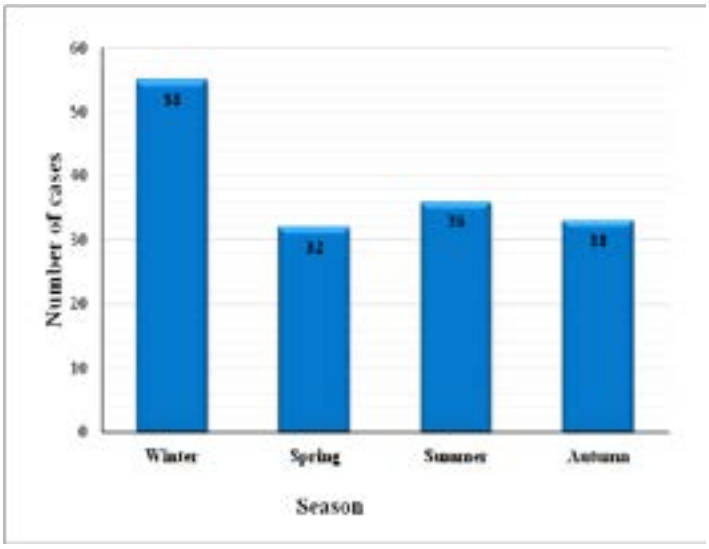

Figure 2: The distribution of all cases of variceal bleeding by season. Case were most frequent in winter and least frequent in June (55 vs 32 cases, P=0.025).

recurrent bleeding is as high as 60%, with a mortality rate of up to 33% [7]. Risk factors for esophageal variceal bleeding include large variceal size, the presence of red wale markings, severe liver disease (Child-Turcotte-Pugh class B/C) and an increased hepatic venous pressure gradient (HVPG) [3]. Despite its excellent diagnostic and prognostic value, the use of HVPG in clinical practice is limited due to several factors such as the invasiveness of the procedure, its availability only in specialized centers, and excessive costs [8]. No biomarker has been identified that predicts elevated HVPG and the associated high risk of esophageal variceal bleeding [9].

Seasonal correlation has been documented in cardiovascular disease (stroke, myocardial infarction and venous thromboembolism) [10]. Circadian rhythmicity in portal blood flow and in portal pressure has also been described [11, 12]. Studies in Japan, Italy, and France [13, 14] have explored seasonal correlation and variceal bleeding,

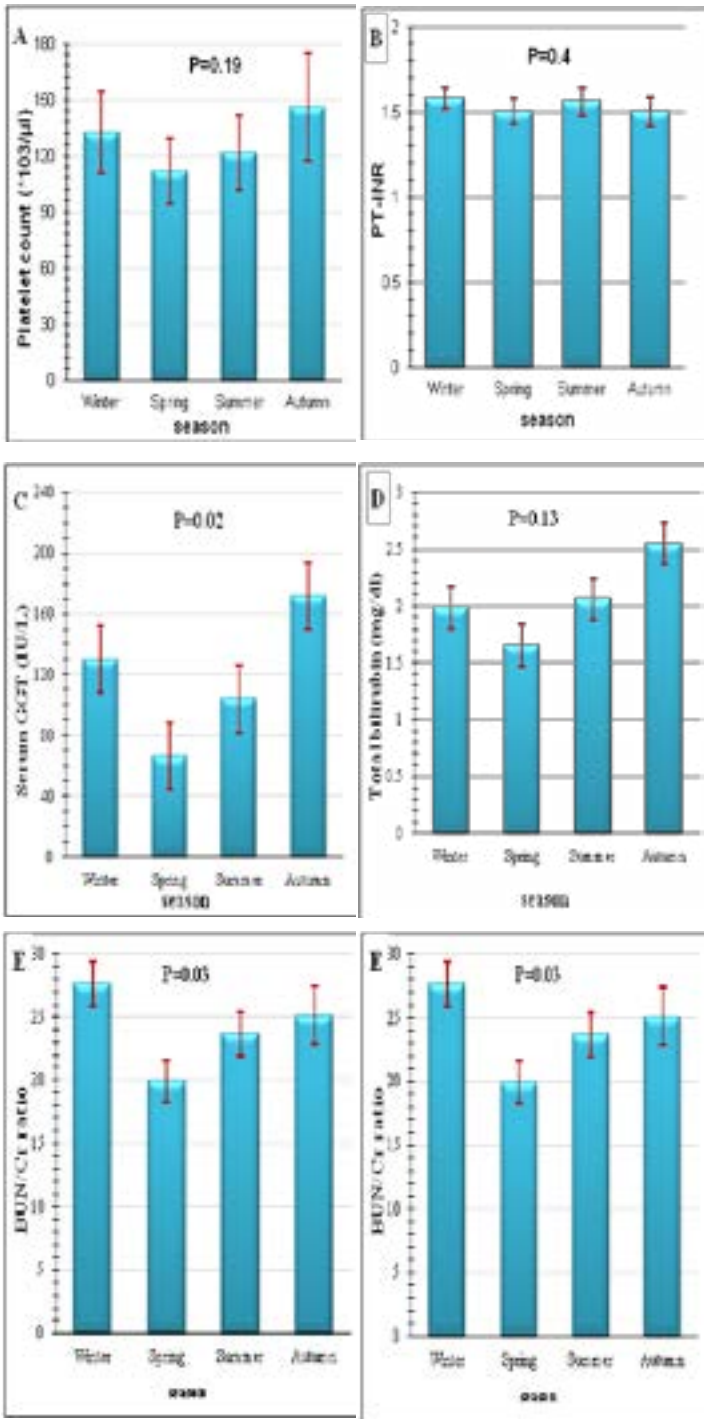

Figure 3: The difference between the four seasons in regard of (A) Platelet count, (B) Prothrombin time - international normalized ratio (PT-INR), (C) total bilirubin level, (D) Serum Gamma-glutamyl transferase (GGT), (E) Blood urea nitrogen to Creatinine (BUN/Cr) ratio, and (F) atmosphere temperature in north Israel.

The winter, the season with the highest incedence of esophageal bleeding, is cherectarized by the lowest mean atmosphere temperature (P<0.001), and the highest BUN/Cr ratio (P = 0.03). Mean GGT levels were lowest in the spring (0.02), the season with the lowest incidence of esophageal bleeding.

Table 1. Clinical Characteristics of Patients with Variceal Bleeding.

n (%)	Variables
156	Total population study
81 (52%)	Men
75 (48%)	Women
64 ± 13 years	Age, mean±SD
	Etiology of cirrhosis
65 (42%)	NAFLD
36 (23%)	HCV
32 (21%)	ALD
23 (15%)	Others
92 (59%)	First episode of variceal bleeding
NAFLD, non-alcoholic fatty liver disease; HCV, Hepatitis C virus; ALD, Alcoholic liver disease	

but the findings remain inconclusive. We do not know of any study performed in Israel that investigated an association of seasonal variation with esophageal variceal bleeding in patients with liver cirrhosis.

The aim of this study was to examine a possible seasonal correlation in the occurrence of esophageal variceal bleeding in the Israeli population, considering the warmer climate in Israel than that in Europe; and to investigate positive and negative predictors of such bleeding.

4. Materials and Methods

This retrospective single-center study was performed at Galilee Medical Center, a tertiary medical center that serves the population of northern Israel. The study was approved by the center's institutional review board (IRB).

Consecutive patients who were admitted to the internal medicine departments, the intensive care unit, and to the departments of general surgery with the diagnosis of "gastro esophageal varices with bleeding" between January 1, 2010 and December 31, 2015.

Study inclusion criteria were:

1) Age older than 18 years
2) The patient had the diagnossis of liver cirrhosis proven by a liver biposy or a non invasive tests such as Transient elastography
3) The patients are admiited to hospital with diagnosis of acute gastro esophageal bleeding that was confirmed by the observation of actively bleeding varices or varices with an adherent clot on emergency endoscopy (performed within 48 hours of admission).

Table 2. The distribution of acute variceal bleeding by season, subgroup analysis.

		Total	Winter	Spring	Summer	Autumn	P Value
Total, n(%)		156	55 (35%)	32 (21%)	36 (23%)	33 (21%)	0.02
Men		81	30	19	17	15	0.049
Women		75	25	13	19	18	0.05
Age, Mean (years)		64	63	65	64	63	
Age > 60		95	33	18	25	19	0.1
Age <60		61	22	14	11	14	0.2
Etiology of cirrhosis	**NAFLD**	65	22	12	16	15	0.05
	HCV	37	15	7	8	7	0.18
	ALD	35	10	10	8	6	0.73
	Others	19	8	3	4	5	0.31
First episode of variceal bleeding		93	35	13	23	22	0.015
Recurrent variceal bleeding		63	20	19	13	11	0.29
MELD score		9.57	9.62	9.75	9.8	9.02	0.83
Mortality		14 (9%)	5 (9%)	4(9%)	2 (5%)	4 (12%)	0.19
NAFLD, non-alcoholic fatty liver disease; HCV, Hepatitis C virus; ALD, Alcoholic liver disease; MELD, Model for End-Stage Liver Disease							

We excluded from the analysis all patients with hepatocellular carcinoma and those treated with antithrombotic agents.

Information accessed from the database included patients' demographic and clinical characteristic, the date of admission, the background etiology of cirrhosis, a history of previous variceal bleeding, and blood tests including liver and renal function tests and parameters of complete blood count. We also received climate data including daily weather records of northern Israel for the study period from the Israel meteorological service (IMS), Bet-Dagan, Israel.

The main aim of this study was to evaluate seasonal variations of variceal bleeding in patients with chronic liver disease. To this end, after the data was collected, all cases were categorized into twelve

1-month intervals and into four 3-month intervals (seasons): winter was defined as January-March, spring as April-June, summer as July-September, and autumn as October-December. The data were analyzed according to month and season.

SPSS (Statistical Package for the Social Sciences) software was used for statistical analysis. Distributions of events according to month and season were first examined for homogeneity in the overall population and then for various subgroups using χ^2 test. Data according to the 4 seasons were further compared using the one-way ANOVA test. A P value < 0.05 was considered significant.

5. Results

A total of 156 patients were diagnosed with acute esophageal variceal bleeding during the study period. Of them, 81 (52%) were male. The mean age was 64 ± 13 years. For 92 patients (59%), the diagnosis was a first episode of variceal bleeding, and for the other 41% of patients they had recurrent esophageal variceal bleeding and all of them received seconday prophylaxis by beta-blockers. Table 1 summarizes demographic and clinical characteristics of the study population.

Esophageal variceal bleeding exhibited a monthly variation (Figure 1) and the occurrence rate peaked in March (13.5% of cases) and the lowest rate was in June (5.7% of cases). Esophageal variceal bleeding exhibited also a seasonal variation (Figure 2) with peak incidence in the winter which was 70% more than that in spring (35% vs 20%, P=0.02). This finding was consistent in most subgroup analyses, including male and female gender (table 2), patients with nonalcoholic fatty liver disease (NAFLD) and patients with first episode of esophageal bleeding. As shown in table 2, the mean age of the patients was similar between groups and also the severity of liver disease, assessed by the Model for End-Stage Liver Disease (MELD) score. While peak incidences were observed in the winter for the etiologies examined, statistical significance was not obtained, apparently due to the small sizes of the subgroups. The total mortality rate was 9%, without significant difference between the groups. In multiple regression analysis, four parameters can explain this variation, the first is NAFLD as etiology of cirrhosis in which the variation was more prominent than other etiologies (P=0.05), the second parameter was gamma-glutamyl transferase (GGT) level (Figure 3), for which the mean was the lowest in the spring, the season with the lowest rate of variceal bleeding (P=0.02), the third parameter was the temperature in northern Israel, which is lowest in the winter (P<0.001), and the fourth parameter was the BUN to Creatinine ratio which was highest in the winter (P=0.03)

6. Discussion

The present study revealed monthly variations in the incidence of esophageal variceal bleeding in patients with liver cirrhosis. January, February and March are the coldest months in Israel and represent the winter season, and according to the results of the current study, the occurrence of esophageal variceal bleeding is highest in the winter (Figure 2). Consistent with these findings, in a large multicenter French study of 13514 cases, Boulay et al found that mortality from variceal bleeding occurred more frequently in winter months (December/January), both in the overall population and in subgroups, according to patient characteristics [14]. In the current study, patients whose variceal bleeding occurred in the winter had a higher BUN/creatinine ratio than did those who bled in other seasons. We do not know of any studies that examined the role of this biomarker in predicting the risk for variceal bleeding and the seasonality of such bleeding. A few studies have suggested a role for the BUN/creatinine ratio in localizing the site of gastrointestinal bleeding [15, 16], but in the current study endoscopic documentation of variceal bleeding in all patients. The question thus arises as to an explanation for the findings. The BUN/creatinine ratio is a marker of dehydration. In case of dehydration, the body reacts with cardiac output redistribution and splanchnic vasoconstriction. Dehydration is a possible explanation for our finding, although no correlation with temperature was revealed. We speculate that in hot months people tend to drink more fluid, thus avoiding dehydration; whereas in the winter, such awareness may be less prominent. Measuring blood, urine osmolality, urine sodium or the fractional excretion of sodium would have enabled confirming or refuting the possibility of seasonal changes in dehydration. Another plausible explanation for the elevated BUN/creatinine ratio in the winter could be increased consumption of a protein-rich diet in this season. However, we have no data on patients' dietary habits. A third possible explanation for the elevated BUN/creatinine ratio in the winter is altered composition of the gut micro biome. Davenport et al demonstrated seasonal variation in human gut micro biome composition [17]. Gut micro flora plays an essential role in the development of cardiovascular diseases including hypertension [18, 19]. Thus, a change in gut flora could also influence portal vein hemodynamics. In our study we did not examine the gut micro biome of the patients.

Our study showed that low temperature can predict increased risk for esophageal bleeding. Increased portal pressure and the formation of esophageal varices were found to correlate with the risk of variceal bleeding [20]; such an increase in portal pressure may be more prominent in the winter. Portal flow and portal pressure have been shown to exhibit a circadian rhythm [7, 11]. The question arises as to whether an increase in portal pressure in the winter as a physiologic

response to low temperature leading in an increased incidence of esophageal variceal bleeding in the winter. Systemic blood pressure has been shown to have seasonal variation and to be increased in the winter [21]. Findings from animal studies suggest that cardiac output and portal pressure may increase during exposure to lower temperature [21]. Peripheral vasoconstriction induced by low temperature may also lead to a shift in blood volume from the body to the splanchnic circulation [23].

We also found that patients who bled in the spring, the season with the lowest rate of esophageal variceal bleeding, had lower levels of serum GGT. Therefore, a low GGT level may predict low risk of bleeding. Considerable evidence shows that GGT may be a surrogate marker of inflammation and oxidative stress [24, 25]. Novel inflammatory biomarkers, such as IL-1β and IL-1Rα, have been shown to correlate significantly with the hepatic venous pressure gradient (HVPG) in compensated cirrhosis [26]. Anamnestic clues for viral infections and levels of inflammatory biomarkers, such as c- reactive protein, erythrocyte sedimentation rate, and interleukin, were not available in our study, so we could not investigate possible associations of infection and inflammation with the risk of esophageal variceal bleeding.

The main limitation of this study is its retrospective design; consequently, valuable data were missing, including information regarding portal vein pressure such as HVPG, liver stiffness and sonographic parameters of the portal vein, dietary habits and the gut micro biome. Such data could be useful for explaining the seasonal variation of variceal bleeding. Another limitation is the small patient population, which did not enable drawing conclusions regarding certain patient subgroups.

In summary, this study provides evidence of seasonal variation of esophageal variceal bleeding in Israeli patients with liver cirrhosis, and increased risk of such bleeding i in the winter season. We suggest that patients with liver cirrhosis and portal hypertension may undergo endoscopy shortly before the winter season.

References

1. Calès P, Pascal JP. Natural history of esophageal varices in cirrhosis (from origin to rupture). Gastroenterol Clin Biol. 1988; 12: 245-254.

2. M Pinzani, M Rosselli, Zuckermann M. Liver cirrhosis. Best Pract Res Clin Gastroenterol. 2011; 25: 281-290.

3. Biecker E. Portal hypertension and gastrointestinal bleeding: diagnosis, prevention and management. World J Gastroenterol. 2013; 19(31): 5035-50.

4. D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: an evidence-based approach. Semin Liver Dis. 1999; 19: 475-505.

5. Garcia-Tsao G, Bosch J. Management of Varices and Variceal Bleeding in Cirrhosis. N Engl J Med. 2010; 362(9): 823-32.

6. Bari K, Garcia-Tsao G. Treatment of portal hypertension. World J Gastroenterol. 2012; 18: 1166-1175.

7. Garcia-Pagan JC, Feu F, Castells A, Luca A, Hermida RC, Rodés J, et al. Circadian variations of portal pressure and variceal bleeding in patients with cirrhosis. Hepatology 1994; 19: 595- 601.

8. Merkel C, Montagnese S. Should we routinely measure portal pressure in patients with cirrhosis, using hepatic venous pressure gradient (HVPG) as guidance for prophylaxis and treatment of bleeding and re-bleeding?Yes! Eur J Intern Med. 2011; 22: 1-4.

9. Saad E, Barhoum M, Assy N. Serum Biomarkers for Evaluating Portal Hypertension. Arch Med. 2016; 8: 4.

10. Saad E, Hoffman R, Saharov G, Brenner B, Nadir Y. Dehydration as a Possible Cause of Monthly Variation in the Incidence of Venous Thromboembolism. Clin Appl Thromb Hemost. 2016; 22(6): 569-74.

11. Alvarez D, Golombek D, Lopez P, Viola L, Heras MDL, Mastai R, et al. Diurnal fluctuations of portal and systemic hemodynamic parameters in patients with cirrhosis. Hepatology. 1994; 20: 1198 -203.

12. Sato G, Matsutani S, Maruyama H, Siasho H, Fukuzawa T, Burioka N. Chronobiological Analysis of Seasonal Variations of Variceal Bleeding. Correspondence. Hepatology. 1998; 28.

13. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W. Prevention and Management of Gastroesophageal Varicies and Variceal Bleeding in Cirrhosis. The American Journal of Gastroenterology. 2007; 102: 2086-2102

14. Boulay F, Herthier F, Dahan C, Albert T: Variations in Variceal Bleeding Mortality and Hospitalization in France. The American Journal of Gastroenterology. 2001; 1881-1887.

15. Snook JA, Holdstock GE, Bamforth J. Value of a simple biochemical ratio in distinguishing upper and lower sites of gastrointestinal haemorrhage. Lancet. 1986; 1: 1064-5.

16. Chalasani N, Clark WS, Wilcox CM: Blood urea nitrogen to creatinine concentration in gastrointestinal bleeding: A reappraisal. Am J Gastroenterol. 1997;92:1796–9.

17. Davenport ER, Mizrahi-Man O , Michelini K, Barreiro LB, Ober C, Gilad Y, et al. Seasonal variation in human gut microbiome composition. PLoS One. 2014; 9(3): e90731.

18. Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, Hazen SL, et al: Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature. 2011; 472(7341): 57-63.

19. Li J, Zhao F. Gut microbiota dysbiosis contributes to the development of hypertension. Microbiome. 2017 1; 5(1): 14.

20. Groszmann RJ, Bosch J, Grace ND, Conn HO, Garcia-Tsao G, Lerner E. Hemodynamic events in a prospective randomized trial of propranolol versus placebo in the prevention of a first variceal bleeding. Gastroenterology 1990; 99: 1401-1407.

21. Brennan PJ, Greenberg G, Miall WE, Thompson SG. Seasonal variation in arterial blood pressure. Br Med J (Clin Res Ed) 1982; 285: 919-23.

22. Bosch J, Pizcueta P, Feu F, Fernández M ,García-Pagán JC. Pathophysiology of portal hypertension. Gastroenterol Clin North Am. 1992; 21: 1-14.

23. Izzo JL Jr, Larrabee PS, Sander E, Lillis LM. Hemodynamics of seasonal adaptation. Am J Hypertens. 1990; 3: 405-7.

24. Lee YJ, Kim JK, Lee JH, Lee HR, Kang DR, Shim JY. Association of serum gamma-glutamyltransferase with C-reactive protein levels and white blood cell count in Korean adults. Clin Chem Lab Med. 2008; 46: 1410-1415.

25. Bo S, Gambino R, Durazzo M, Guidi S, Tiozzo E, Pagano GF: Associations between gamma-glutamyl transferase, metabolic abnormalities and inflammation in healthy subjects from a population-based cohort: a possible implication for oxidative stress. World J Gastroenterol. 2005; 11: 7109-7117.

26. Buck M, Garcia-Tsao G, Groszmann RJ, Stalling C, Grace ND, Chojkier M. Novel Inflammatory Biomarkers of Portal Pressure in Compensated Cirrhosis Patients Hepatology. 2014; 59(3): 1052-1059.