Modelling Factors Causing Mortality in Oesophageal Varices Patients in King Abdul Aziz University Hospital

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Abstract

Objectives: The objective of this study is to reach a model defining factors precipitating short survival in patients with oesophageal varices and improving the understanding of such factors. Models would help to prioritize the clinical goals and intervention for saving the lives of patients.

Methods: Retrospective analysis of all patients admitted to King Abdul Aziz University Hospital who had been diagnosed with oesophageal varices. The patients' demographics, disease history, physical examination, viral infections, parasitic infections, blood pictures, cancer biomarkers, liver enzymes and bleeding details were collected, tested for correlation with mortality to formulate a model.

Results: A total of 148 patients were included in this study. 37 clinical variables were studied only 15 factors were found to have a statistical significance. These factors were PT (RC=0.17338 P-value 0.00011), APTT (RC=0.07916, P-value 0.00002), haemoglobin level (RC=-0.44748, P-value <0.0001), WBC (RC = 0.22255, P-value 0.00001), serum albumin level (RC=-0.12953, P-value 0.00001), serum creatinine (RC=0.01483, P-value 0.00002), at least one incidence of encephalopathy (RC=1.80500, P-value 0.00014), total bilirubin (RC=0.01371, P-value 0.00016), direct bilirubin (RC=0.01298, P-value 0.00357, serum AST (RC=0.00914, P-value 0.00462), presence of at least bleeding event (RC=1.03373, P-value 0.00613), ascites grade I (RC=-1.57435, P-value 0.00967), SBP (RC=1.47216, P-value 0.01581), platelets count (RC=0.00398, P-value 0.03476) and oesophageal varices (RC = -1.42139, P-value 0.03673). Only 5 factors were likely to affect the mortality status. These factors were encephalopathy, spontaneous SBP, bleeding, ascites and grade of oesophageal varices. Six models were then formulated.

Conclusion: These models should be retested in larger study groups to test their reliability in order to use them as surrogate end point in future clinical studies.

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Received: 20 April 2009
Accepted: 04 May 2009

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Bahlas S. *OMJ*. 24, 199-203 (2009); doi:10.5001/omj.2009.39

Introduction

King Abdul-Aziz University Hospital (KAUH) is a tertiary hospital where a lot of complicated cases are referred to. From its registry, a retrospective analysis was conducted to assess the esophageal cases received over 2007-2008. During daily practice, it has been noticed that mortality is high in esophageal patients. This study attempts to measure the problem and to evaluate the reasons for recorded mortality.

Gastroesophageal varices are considered as one the most severe and frequent cause of gastrointestinal bleeding in cirrhotic patients, leading to death in 5% to 8% of patients during the first 48 hours.[1]

In several research studies, oesophagogastric varices account for 60% to 80% of first bleeding in patients with portal hypertension.[2] Early rebleeding is significantly related to death within six weeks[3]. Amirtano found that peptic ulceration and reflux oesophagitis are some of the reasons for acute upper gastrointestinal bleeding in patients with cirrhosis Guo et al had failed in comprehensive review to establish a relationship between the preventions of gastric bleeding and the improvement survival status based on therapies.[5] It is widely accepted that clinicians make practical decisions, often on the basis of inadequate information. Decisions about treatment should preferably be taken based on the results of randomised trials.[6-7]

Gøtzsche and Hróbjartsson tried to establish a relationship between mortality and the use of Somatostatin analogues in acute bleeding oesophageal varices. Unfortunately the evidence found was that Somatostatin analogues had significantly reduced the blood transfusion with undetectable impact on mortality.[8]

All the above mentioned studies are driving more efforts to modulate the relationship between oesophageal varices and mortality in KAUH. These modalities can be used in clinical studies combined end-point instead of a single factor like direct mortality. This module is also helpful in allocating the intervention type for each patient. Patient stratification in future research or in clinical practice may be of importance but it can only be effectively implemented once a reliable robust model has been established.

Methods

This is a retrospective analysis of all patients admitted to King Abdul

Aziz University Hospital diagnosed with oesophageal varices. The patients' demographics, disease history, physical examination, viral infections, parasitic infections, blood pictures, cancer biomarkers, liver enzymes and bleeding details were collected. These variables were correlated against mortality collectively and separately to find out a possible relationship with mortality.

The patients' demographics are presented in a descriptive manner showing the mean and standard deviation for continuous variables. T-test or Chi-square tests were used to test the difference between two cirrhotic and non-cirrhotic groups. Since the time factor can not be measured or determined due to the non-timely planned referral to the hospital, the Cox-regression can not be applied and logistic regression has been used to define the relationship for each variable and mortality.

A total of 148 patients were included, 71.62% (106 patients) had died. 37 clinical variables were studied. Theses variables are gender, age, nationality, liver cirrhosis, hepatocellular carcinoma HCC, portal vein thrombosis PVT, bleeding incidence, oesophageal ascites grade, encephalopathy, spontaneous bacterial peritonitis SBP, haemoglobin, platelets count, white blood corpuscles WBC count, direct bilirubin (Bilirubin D), total bilirubin (Bilirubin T), serum albumin, serum alkaline phosphatise ALK, aspertate aminotransferase AST, alanine aminotransferase ALT, serum creatinine, prothrombine time PT, activated partial thromboplastim time APTT, alfa –fetoprotein level, splenectomy, infection with hepatitis C virus, infection with hepatitis B virus, infection with hepatitis E virus, Bilharziasis, autoimmune hepatitis, cryptogenic lever, grade of oesophageal varices, portal hypertension gastropathy, hemochromatosis, and Child-Pugh Score for cirrhosis.

Results

Patient categorization based liver cirrhosis are presented in Table 1. There was no statistical difference among the 2 categories.

Table 1: Patient Demographics

Parameters	Demographics	%	Cirrhotic (N=106)	Non-Cirrhotic (N=41)
Gender	Female	26.35	23.58	34.15
	Male	73.65	76.42	65.85
Origin	Non-Saudi	60.96	62.50	56.10
	Saudi	39.04	37.50	43.90
HCC	Absent	93.2	92.38	95.12
	Present	6.8	7.62	4.88
Portal Vein Thrombosis	Absent	97.96	97.14	100
	Present	2.04	2.86	0
Bleeding	Absent	62.76	63.46	62.50
	Present	37.24	36.54	37.50
Ascites	Absent	25.6	28.87	14.29
	e.controlled*	35.2	36.08	32.14
	tense	39.2	35.05	53.57
Encephalopathy	Absent	78.69	79.57	75.86
	Present	21.31	20.43	24.14
SBP	Absent	89.26	92.31	80.00
	Present	10.74	7.69	20.00
Mortality	Present	71.62	73.58	65.85
	Absent	28.38	26.42	34.15
HCV	Absent	58.78	62.26	48.78
	Present	41.22	37.74	51.22
HBV	Absent	88.51	85.85	95.12
	Present	11.49	14.15	4.88
Child-Pugh Grade	Grade A	NA	3.77	NA
	Grade B	NA	25.47	NA
	Grade C	NA	70.75	NA

Age (Years)	Mean±SD	50.98	51.59±18.42	49.57±16.35
Haemoglobin	Mean±SD	13	13.82±28.58	10.96±2.66
Platelets	Mean±SD	125.17	126.88±96.69	122.64±88.85
WBC	Mean±SD	7.24	7.13±5.11	7.65±5.70
Bilirubin T	Mean±SD	63.73	65.25±102.07	60.76±108.02
Bilirubin D	Mean±SD	64.96	66.91±91.59	62.57±123.54
Serum Albumin	Mean±SD	25.76	25.61±8.21	26.01±8.32

*e.controlled = Easily Controlled, HCC: Hepatocellular Carcinoma, SBC: Spontaneous Bacterial Peritonitis,

Table 2: Logistic Regression Test Results for All Studied Variables

Parameter	Regression Coefficient (Beta)	Standard Error	Wald Z-Value (Beta=0)	Wald P-value	Odds Ratio Exp(B)
Gender (Female)	0.18664	0.42275	-0.441	0.65886	0.82974
Age	0.00980	0.01102	0.890	0.37373	1.00985
Nationality (Saudi)	-0.00098	0.37751	0.003	0.99794	1.00098
Cirrhosis	-0.36772	0.39623	0.928	0.35338	1.44444
Hepatocellular Carcinoma	0.99425	0.66108	-1.504	0.13259	0.37000
Portal Vein Thrombosis	0.22801	1.23859	-0.184	0.85394	0.79612
Bleeding	1.03373	0.37717	-2.741	0.00613	0.35568
Ascites	-1.57435	0.60844	2.588	0.00967	4.82758
Encephalopathy	1.80500	0.47503	-3.800	0.00014	0.16447
SBP	1.47216	0.61003	-2.413	0.01581	0.22943
Haemoglobin	-0.44748	0.09643	4.640	<0.0001	1.56436
Platelets	0.00398	0.00189	-2.111	0.03476	0.99602
WBC Count	0.22255	0.05103	-4.361	0.00001	0.80047
Bilirubin T	0.01371	0.00363	-3.781	0.00016	0.98638
Bilirubin D	0.01298	0.00445	-2.914	0.00357	0.98710
Albumin	-0.12953	0.02951	4.390	0.00001	1.13830
ALK	0.00128	0.00165	-0.779	0.43610	0.99872
AST	0.00914	0.00323	-2.833	0.00462	0.99090
ALT	-0.00274	0.00495	0.555	0.57911	1.00275
Serum Creatinine	0.01483	0.00346	-4.282	0.00002	0.98528
Prothrombin Time	0.17338	0.04472	-3.878	0.00011	0.84081
Partial Thromboplastim Time	0.07916	0.01870	-4.234	0.00002	0.92389
α-Fetoprotein	0.00299	0.00165	-1.812	0.07006	0.99701
Splenectomy	0.46536	0.59672	-0.780	0.43547	0.62791
Hepatitis C Virus	-0.18130	0.37360	0.485	0.62749	1.19877
Hepatitis B Virus	0.36422	0.54395	-0.670	0.50312	0.69474
Bilharziasis	-1.02808	0.78274	1.313	0.18903	2.79570
Autoimmune Hepatitis	-0.90016	1.09593	0.821	0.41144	2.46000
Cryptogenic Lever	-0.09531	0.61461	0.155	0.87676	1.10000
Oesophageal Varics G0	-1.60944	1.21890	1.320	0.18670	5.00000
Oesophageal Varics G1	-0.91629	0.67876	1.350	0.17703	2.50000
Oesophageal Varics G2	-1.42139	0.68048	2.089	0.03673	4.14286
Oesophageal Varics G3	-0.94098	0.61041	1.542	0.12318	2.56250
Portal Hypertension Gastropathy	-0.03555	0.37183	0.096	0.92383	1.03619
Hemochromotosis	-9.28655	164.26086	0.057	0.95492	10000+

ALK:Alkaline Phosphatase, ALT: Alanine Aminotransferase, APTT: Activated Partial Throboplastin time, AST: Aspartate Aminotransferase, AUC: Area under the Curve, HCC: Hepatocellular Carcinoma: PT: Prothrombin Time, PVT: Portal Vein Thrombosis, RC: Regression Coefficient, ROC: Receiver Operating Characteristic, WBC: White Blood Cells

Fifteen factors recorded statistical significance results. These factors were: PT, APTT, haemoglobin, WBC Count, serum albumin, serum ceatinine, encephalopathy, Bilirubin T, Bilirubin D, AST, bleeding, ascites grade absence, SBP, platelets, Oesophageal varices grade II.

It is noteworthy that 11 factors had shown prominent effect on mortality (i.e. RC >0.5 or <-0.5) while only five out these eleven were statistically significant. These five factors are encephalopathy, SBP, bleeding, ascites, and oesophageal varices. These factors are displayed in ROC curves to find the applicability to be used as surrogate for mortality.

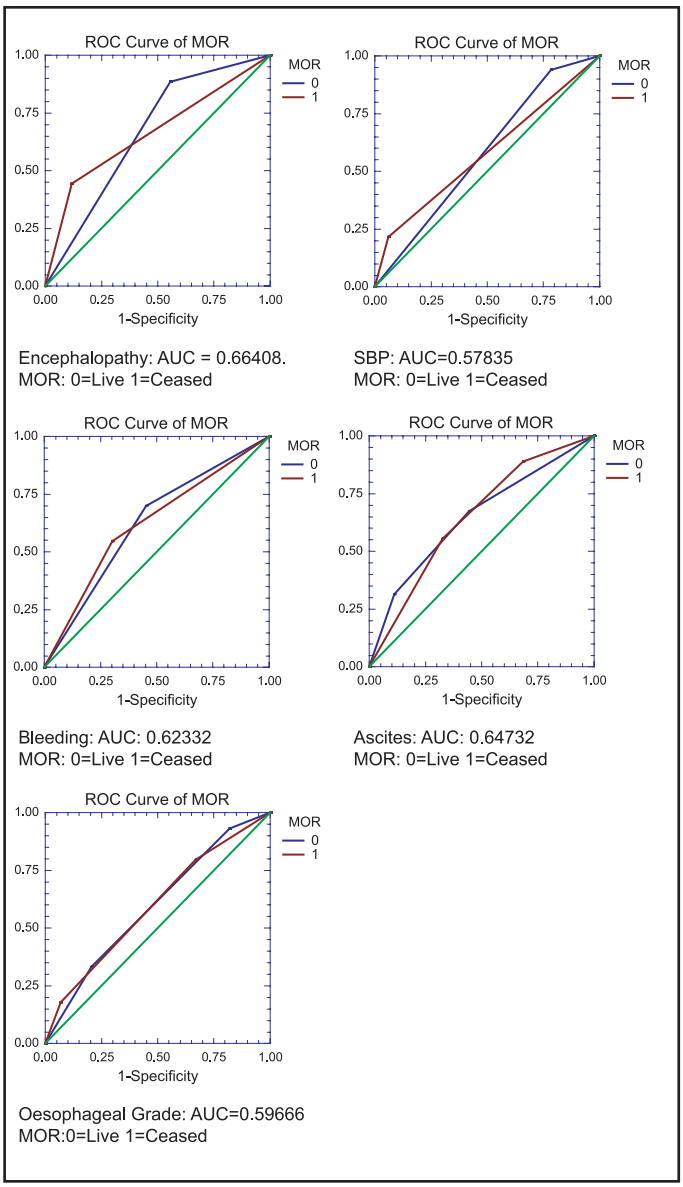

Figure 1: ROC Curves for Encephalopathy, SBP, Bleeding, Ascites, Oesophageal varices

All the tested five factors had shown AUC >0.5 confirming the ability of diagnostic usage. These factors have been tested for formulating a model. The models suggested for testing are:

Model 1: The five factors were tested together Bleedding-Ascites-encephalopathy-SBP-Oesophageal Varices Grade. The recorded AUC for Model was 0.82 which indicates a very competent tool to expect mortality. This model uses five variables where a difficulty can be anticipated during the clinical practice. Several models can also be studied based on omission of one variable and keeping the most relevant variables, consequently other five models can be reached. Figure 1 shows the ROC curves for each tested model.

Model 1 formula: 3.6+ 0.6*ascites-1.3*Bleedding-1.6*encephalopathy -0.2*OV_grade -0.3*SBP

Model 2: Bleedding-Ascites-SBP-Oesophageal Varices Grade. In this model encephalopathy has been omitted which gives AUC 0.795.

Model 2 formula: Formula: 0.5 + 0.8*ascites-1.0*Bleedding -.02*OV_grade -.8*SBP

Model 3: Bleedding-ascites-Encephalopathy-OV Grade. In this model SBP has been omitted which gives AUC 0.806.

Model 3 formula: 3.1 + 0.7*ascites -1.4*Bleedding -1.7*encephalopathy-0.2*OV_grade

Model 4: Bleedding-SBP-OV Grade Encephalopathy. In this model Ascites has been omitted which gives AUC 0.796.

Model 4 formula: 6.1 -1.3*Bleedding -2.0*encephalopathy -0.02*OV_grade-.6*SBP

Model 5: Bleedding-ascites-Encephalopathy-SBP. In this model oesophageal varices has been omitted which gives AUC 0.792 and

Model 5 formula: 3.2 + .5*ascites-1.3*Bleedding-1.4*encephalopathy-.4*SBP

Model 6: Ascites-OV grade-Encephalopathy-SBP. In this model bleeding has been omitted which gives AUC 0.769.

Model 6 formula: 1 + .8*ascites -1.5*encephalopathy-.1*OV_grade-.5*SBP

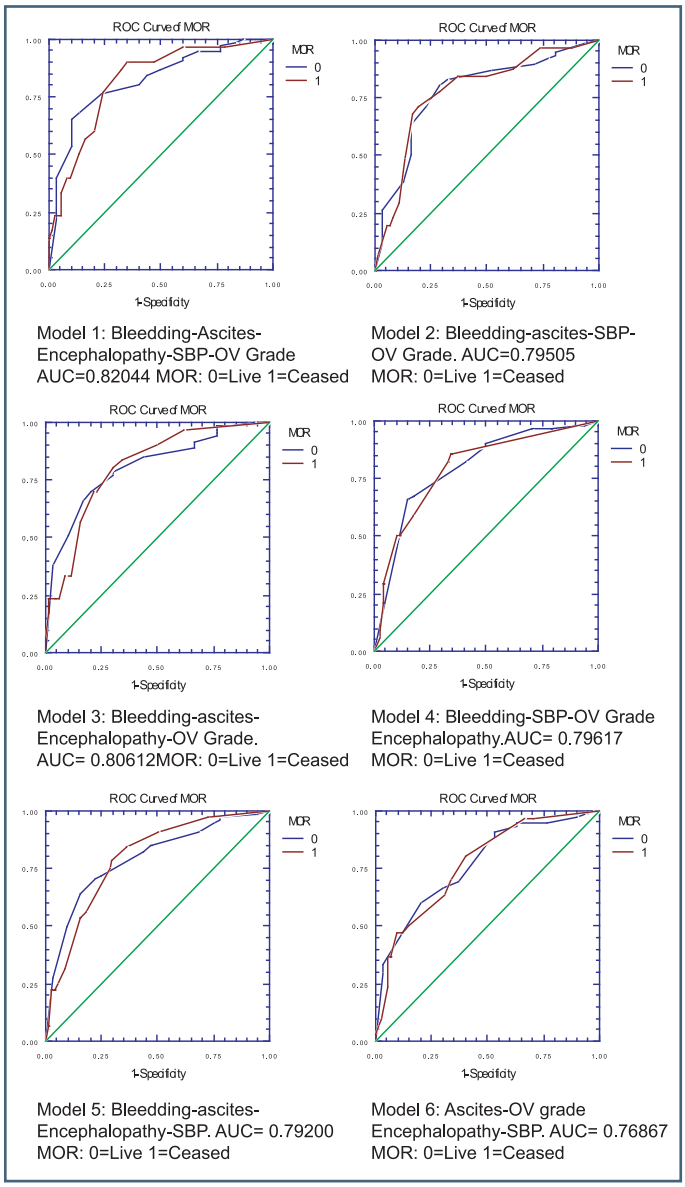

Figure 2: ROC Curves for Encephalopathy, SBP, Bleeding, Ascites, Oesophageal varices

Discussion

Because the nature of a tertiary hospital where patients are referred when their status is complicated, the primary prophylaxis were not possible to measure. Consequently, 37 variables were used for assessing mortality. Due to the difference in the aetiology of portal hypertension, patients were categorized into cirrhotic and non-cirrhotic groups. This categorization did not show any clear difference in patients' demographics meanwhile the mortality in both groups seemed very similar.

Upon statistical testing of all 37 variables,there was no significant difference between the cirrhotic and non-cirrhotic patients (Table 1). Several studies tried to find a mathematical relationship controlling patient survival.[1-8] This study had collected all the possible and available variables recorded during the period 2007-2008 in order to find all possible relationships. The results obtained showed that mortality is dependant on multiple factors. The main prominent and statistical significant factors were five factors. These five factors were used to create model 1.

Although Model 1 can be used a good surrogate for mortality expectation, to use the five factors during daily clinical practice is not very easy. The alternatively tested models are very comparable to Model 1. Consequently all of them can be used almost successively. The impact of the oesophageal varices is very minimal in Models 2 and 4. This will help clinicians and researchers in using formulas without needing to assess the grade of the oesophageal varices as well. Comprehensive reviewers recommended the use of randomised clinical trials after the absence of a robust relationship of with mortality with oesophageal bleeding.[5,7]

Conclusion

These formulas can be applied in designing clinical studies as a surrogate endpoint. These models should be tested on a larger group of patients to ensure their reliability.

Acknowledgements

The authors reported no conflict of interest and no funding has been received on this work.

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