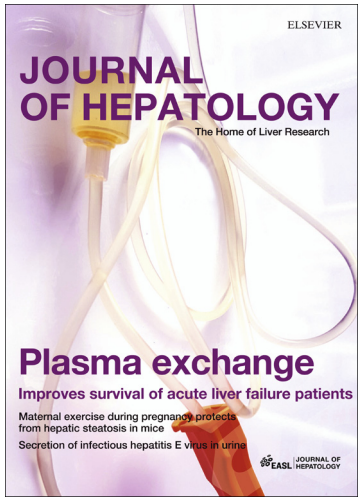


Validation of the Baveno Vi Criteria to Identify Low Risk Cirrhotic Patients not Requiring Endoscopic Surveillance for Varices

James Maurice, Edgar Brodkin, Frances Arnold, Annalan Navaratnam, Heidi Paine, Sabrina Khawar, Ameet Dhar, David Patch, James O'Beirne, Raj Mookerjee, Massimo Pinzani, Emmanouil Tsochatzis, Rachel H. Westbrook

PII: S0168-8278(16)30316-6
DOI: http://dx.doi.org/10.1016/j.jhep.2016.06.021
Reference: JHEPAT 6168

To appear in: *Journal of Hepatology*

Received Date: 22 January 2016
Revised Date: 5 June 2016
Accepted Date: 7 June 2016

Please cite this article as: Maurice, J., Brodkin, E., Arnold, F., Navaratnam, A., Paine, H., Khawar, S., Dhar, A., Patch, D., O'Beirne, J., Mookerjee, R., Pinzani, M., Tsochatzis, E., Westbrook, R.H., Validation of the Baveno Vi Criteria to Identify Low Risk Cirrhotic Patients not Requiring Endoscopic Surveillance for Varices, *Journal of Hepatology* (2016), doi: http://dx.doi.org/10.1016/j.jhep.2016.06.021

Title Page

VALIDATION OF THE BAVENO VI CRITERIA TO IDENTIFY LOW RISK CIRRHOTIC PATIENTS NOT REQUIRING ENDOSCOPIC SURVEILLANCE FOR VARICES

James Maurice[1,2]; Edgar Brodkin[1]; Frances Arnold[1]; Annalan Navaratnam[1]; Heidi Paine[2]; Sabrina Khawar[1]; Ameet Dhar[2]; David Patch[1]; James O'Beirne[1]; Raj Mookerjee[1,3]; Massimo Pinzani[1,3]; Emmanouil Tsochatzis[1,3]; Rachel H Westbrook[1]

[1] Department of Hepatology, Royal Free Hospital NHS Trust
[2] Department of Hepatology, Imperial College Healthcare NHS Trust
[3] Institute for Liver and Digestive Health, University College London

Corresponding Author:
Dr Rachel Westbrook
Department of Hepatology, 8 South Office, Royal Free Hospital, Pond St, London NW3 2QG
Tel: 020 7794 0500 ext 38097 Fax: 020 7472 6226
Rachel.westbrook@nhs.net

Key Words: Portal hypertension, oesophageal varices, non- invasive investigations, transient elastography, cirrhosis

Abbreviations:
AUROC: Area under the receiver operator curve
HVPG: Hepatic venous pressure gradient
TE: Transient elastography
LSM: Liver stiffness measurement
kPa: Kilopascals
OGD: Oesophagogastroduodenoscopy
cACLD: Compensated Advanced Chronic Liver Disease
LRV: Low risk varices
HRV: High risk varices
INR: International Normalised Ratio
HCV: Hepatitis C
ALD: Alcohol related liver disease
NAFLD: Non alcoholic fatty liver disease
HBV: Hepatitis B
PPV: Positive predictive value
NPV: Negative predictive value
LR+: positive likelihood ratio
LR-: negative likelihood ratio

Word Count: 4078

6 Tables, 2 Figures, 1 Supplementary Figure

Conflict of interest: Nothing to declare

Financial support: there was no financial support given for this study.

Author's Contributions:
JM: collected data, analysed data, wrote the manuscript, approved final manuscript.

EB, FA, AN, HP, SK: collected data and contributed to the drafting and final approval of the manuscript.
AD, JO'B, DP, MP, RM, ET: provided data and contributed to the drafting and final approval of the manuscript.
RW: Provided overall oversight of the study, analysed the data, contributed to the drafting and final approval of the manuscript.

Abstract

Background: The Baveno VI guidelines propose that cirrhotic patients with a liver stiffness measurement (LSM) <20kPa and a platelet count >150000/μL can avoid screening endoscopy as their combination is highly specific for excluding clinically significant varices. The aim of the study was to validate these criteria.

Methods: Transient elastography data was collected from two institutions from 2006-2015. Inclusion criteria were a LSM ≥10kPa and an upper gastrointestinal endoscopy within 12 months, with a diagnosis of compensated chronic liver disease. Exclusion criteria were porto-mesenteric-splenic vein thrombosis and non-cirrhotic portal hypertension. Varices were graded as low risk (grade <2) or high risk (grade ≥2).

Results: The study included 310 patients (169 (55%) hepatitis C, and 275 (89%) Child Pugh A). Varices were present in 23% cases, with 5% prevalence of high risk varices. Overall 102/310 (33%) met the Baveno VI criteria. Within this group 11% had varices and 2% had high risk varices, representing 2/15 (13%) of all high risk varices. The Baveno VI criteria gave a sensitivity 0.87, specificity 0.34, positive predictive value 0.06, negative predictive value 0.98, positive likelihood ratio 1.31 and negative likelihood ratio 0.39. The AUROC for LSM and platelet count combined was 0.746.

Conclusions: The Baveno VI criteria performed well correctly identifiying 98% of patients who could safely avoid endoscopy.

Word count: 213

Lay Summary

This study examines the effectives of a recent set of guidelines published by the Baveno VI conference, which states that patients with chronic liver disease and a low liver stiffness (<20kPa) and high platelet count (>150) are at low risk of having varices and do not need a screening endoscopy. Varices are a complication of cirrhosis, confer a risk of serious bleeding, and can be diagnosed and treated by endoscopy. Our study reviewed the clinical records of patients who have had liver stiffness scans and endoscopy over a 9 year period at two hospitals. The results show that only about 2% of patients who meet the Baveno VI criteria will be miss classified as not having varices.

Introduction

Gastroesophageal varices occur as a consequence of portal hypertension and are a major cause of morbidity and mortality due to the risk of haemorrhage. In cirrhosis raised portal pressures initially develop as a result of advanced fibrosis and deranged liver architecture, but as liver disease progresses additional haemodynamic factors, such as splanchnic vasodilatation and hyperdynamic circulation, become increasingly important (Vizzutti et al. 2007). Portal pressures have traditionally been measured using hepatic venous pressure gradient (HVPG), and an HVPG ≥ 10mmHg confers increased risk of developing gastroesophageal varices (Groszmann et al. 2005). HVPG has been shown to correlate well with the presence and size of varices (Wadhawan et al. 2006), however measuring portal pressures by HVPG is invasive and limited to the centres with the relevant expertise.

Over the last decade transient elastography (TE) has become a widely used, non-invasive measure of liver stiffness and fibrosis. Following initial studies showing its accuracy in diagnosing significant fibrosis its clinical applications have been widened. The use of TE as a surrogate marker of portal hypertension has been demonstrated by liver stiffness measurement (LSM) correlating well with portal pressures up to a HVPG of 10-12mmHg (Vizzutti et al. 2007)(Bureau et al. 2008). Subsequent data has shown that TE is of potential benefit in the non- invasive diagnosis of varices, especially when TE is combined with other markers such as platelet count and spleen size (Berzigotti et al. 2013).

A major limitation to implementing these tests into clinical practice for diagnosing gastroesophageal varices has been an inadequate specificity. As a result the diagnostic strength of non- invasive investigations such as TE have not yet been sufficient to replace endoscopy in the diagnosis of varices (Shi et al. 2013) (EASL 2015), and all patients with

cirrhosis currently require routine surveillance with frequent oesophagogastroduodenoscopy (OGD).

The promising sensitivity and negative predictive value of TE, especially in combination with other non- invasive markers, means these investigations may be more effective tools at identifying low risk cirrhotic patients who can be safely 'ruled out' of needing an endoscopy. The recent Baveno VI guidelines acknowledge this application and recommend that in patients with compensated advanced chronic liver disease (cACLD) a LSM <20Kpa and a platelet count > 150,000 cells/μL have a very low risk of having varices requiring treatment and therefore do not require screening endoscopy. They advise longitudinal follow-up of such patients by annual repetition of TE and platelet count with the guidance that if liver stiffness increases or platelet count declines to within the recommended values, these patients should undergo screening OGD (de Franchis 2015).

In this retrospective cross-sectional cohort study, we reviewed all patients over a nine year period at two centres who have undergone clinical, laboratory, TE and endoscopic evaluation of portal hypertension. The primary aim was to validate the recently proposed Baveno VI criteria and assess their sensitivity at accurately identifying those patients who can safely avoid screening endoscopy. Secondary aims were to assess if the criteria had similar sensitivities across all aetiologies of chronic liver disease, given the majority of published data is from patients with viral hepatitis, and to identify if alternative LSM or platelet parameters should be recommended.

Methods

Study Population

This is a retrospective cohort study. Transient elastography data collected from two institutions from November 2006 - September 2015 were analysed. All patients with a LSM ≥ 10kPa were selected. Additional inclusion criteria were an OGD within 12 months of TE, and a diagnosis of chronic liver disease. Exclusion criteria were decompensated disease

(defined as Child Pugh C disease or Child Pugh B with evidence of ascites, encephalopathy or previous variceal haemorrhage), current use of non- selective beta- blockers, porto-mesenteric-splenic vein thrombosis, and non-cirrhotic portal hypertension. A sub-analysis of all patients with OGD within 6 months of TE was also performed.

Transient Elastography

All TE was performed using Fibroscan© (Echosens, Paris) by experienced practitioners at two large specialist centres who follow conventional practice. Patients were fasted for two hours before the procedure. All patients were examined in the standard way with the right lobe of the liver accessed by the patient lying in the dorsal cubitus position and maximal abduction of the right arm. Ten valid measurements were obtained and a median LSM value (kPa) generated. Inadequate LSM (defined by interquartile range >30% and success <60%) were excluded.

Assessment of varices

All patients had an OGD within 12 months of the TE. Gastroesophageal varices were defined as low risk varices (LRV) or high risk varices (HRV). For the purpose of this study all varices that were described as < grade 2 were defined as LRV. Conversely all oesophageal varices described as ≥ grade 2, and any gastric varices, were defined as HRV. This differentiation was made as all varices classified as high risk in this way would be deemed clinically significant and require treatment in standard clinical practice.

Laboratory Investigations

Laboratory investigations were collected, including platelets, bilirubin, alanine aminotransferase, aspartate aminotransferase, albumin, international normalised ratio (INR), sodium and creatinine.

Statistical analysis

Demographic and laboratory data was summarised and compared between patients with and without HRV. Continuous variables were reported as medians with interquartile range, and compared using Mann-Whitney test. The variables of LSM and platelet count were compared to the binary outcome measure of the presence of HRV. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-) were calculated as per the cut offs recommended by Baveno VI (de Franchis 2015). AUROC values were generated for the presence of HRV, using the variables of LSM, platelet count and the two variables combined.

Statistics were performed using the software packages SPSS.

Results

Study population

Over the study period 12331 transient elastography (TE) scans were performed. After excluding inadequate scans, values <10kPa, and multiple scans on the same patient and scans without an OGD within 12 months, 391 cases remained. Of these, a further 81 were excluded: n=10 non-cirrhotic portal hypertension, n=5 portal/mesenteric/splenic vein thrombosis, n=13 current use of non- selective beta blockers, n=53 decompensated disease. In total 310 patients were included in the study (Figure 1).

Demographic data

Of the 310 cases that met the inclusion criteria for the study, 209 (67%) were male and 101 (33%) female. The aetiology of the underlying liver disease was hepatitis C (HCV, n=169 (55%)), alcohol- related liver disease (ALD, n=40 (13%)), non-alcoholic fatty liver disease (NAFLD, n=42 (14%)), Hepatitis B/D (HBV, n=24 (8%)), and other (n=35 (11%): ALD/HCV (n=5), HBV/NAFLD (n=1), HBV/HCV (n=2), ALD/NAFLD (n=2), drug reaction (n=2), cryptogenic (n=4), Gaucher's/HCV (n=1), Gaucher's (n=1), haemochromatosis (n=2), haemochromatosis/HCV (n=1), sarcoidosis (n=1), sarcoidosis/HBV/HCV (n=1), autoimmune

hepatitis (n=2), primary biliary cholangitis (n=4), primary sclerosing cholangitis (n=5), overlap syndrome (n=1)). One case with ALD had alcoholic hepatitis at the time of transient elastography, with a LSM 16.8kPa. The majority of cases were Child Pugh A (n=275 (89%)), with 35 cases (11%) Child Pugh B. Median MELD score was 7. The above data is summarised in Table 1.

Varices were present in 18% of the population studied (n=57); 15 patients (5%) had HRV. Two cases had high risk stigmata with red wale signs. With respect to LSM, 167 (54%) cases had a LSM <20kPa, and 143 (46%) cases had a LSM ≥ 20kPa. In laboratory tests 151 (49%) cases had platelets >150x10^3/ml, and 159 (51%) had platelets ≤150x10^3/ml (Table 1, 2a and 2b).

Liver stiffness measurement as a predictor of varices

The median LSM in our cohort was 18.4kPa. As expected liver stiffness measurement was significantly higher in patients with HRV than in those without HRV (26.0kPa vs 18.4kPa, p<0.015). In the cases with LSM <20kPa, 23/167 (14%) had any varices, of which 5 (3%) were HRV. Of the cases with LSM ≥20kPa, 49/143 (34%) had any varices, of which 10 (7%) had HRV (Table 2a). Overall for identifying HRV, LSM cut- off of 20kPa had a sensitivity of 0.67, specificity 0.55, positive predictive value (PPV) 0.07, negative predictive value (NPV) 0.97, positive likelihood ratio (LR+) 1.48 and negative likelihood ratio (LR-) 0.61 (Table 3a). The AUROC for LSM as an independent variable was 0.686 (Supplementary Fig 1).

Platelet value as a predictor of varices

The median platelet count in our cohort was 147000/µL, and was not significantly lower in patients with HRV than in those without HRV. In cases with platelets >150000/µL, 22/151 (15%) had any varices, and of these 6 (4%) were HRV. In cases with platelets ≤150000/µL, 50/159 (31%) had any varices, of which 9 (6%) were HRV (Table 2a). Overall for identifying

HRV, platelet count cut-off of 150000/μL had a sensitivity of 0.60, specificity 0.49, PPV 0.06, NPV 0.96, LR+ 1.18, LR- 0.81 (Table 3a). The AUROC for platelets as an independent variable was 0.599 (Supplementary Fig 1).

Baveno VI Criteria as a predictor of varices

The Baveno VI consensus guidelines combine LSM < 20kPa and platelet count >150000/μL. In this cohort, 102/310 (33%) cases met these criteria, of whom 11 (11%) had any varices and 2 (2%) had HRV. Among the 208/310 (67%) cases that fell outside of the Baveno VI criteria, 61/208 (29%) had any varices and 13 (6%) had HRV (Table 2a). Combining LSM and platelet count using the recommended cut-off values to detect HRV gives a sensitivity 0.87, specificity 0.34, PPV 0.06, NPV 0.98, LR+ 1.31, LR- 0.39 (Table 3a). The AUROC for the combination of LSM and platelets was 0.746 (Supplementary Fig 1). Using the Baveno VI guideline 2/15 (13%) of HRV were missed (Figure 2). The LSM and platelet count of these cases were 16.8kPa / 380000/μL and 17.6kPa / 160000/μL respectively. Both cases had grade 2 oesophageal varices and compensated cirrhosis secondary to HCV.

Impact of aetiology on diagnostic accuracy

Out of the 15 cases with HRV, 11 had viral hepatitis and 2 cases had ALD and NAFLD. In a sub analysis by aetiology, the Baveno VI guidelines in viral hepatitis had a sensitivity 0.82, specificity 0.28, PPV 0.06, NPV 0.96, LR+ 1.13 and LR- 0.66; in NAFLD/ ALD, they had a sensitivity 1.00, specificity 0.45, PPV 0.04, NPV 1.0, LR+ 1.82 and LR- 0.00 (Table 4). AUROC for TE, platelets and the two variables combined in viral hepatitis was 0.633, 0.675 and 0.749 and in ALD/NAFLD were 0.924, 0.534 and 0.927 respectively (Supplementary Fig 1).

Impact of Time between OGD and Transient Elastography

The above analysis was repeated in a population restricted to patients who had an OGD within 6 months of transient elastography. This included a slightly smaller (n=219) cohort with similarly mixed aetiology (HCV n=118). In this analysis, 66/219 patients met BAVENO VI criteria for avoiding screening endoscopy, of whom 1 case had high risk varices. The diagnostic performance of the BAVENO VI criteria was similar in this sub-group as for the whole study population (Table 2b and 3b).

Discussion

In this large dual centre cross- sectional cohort study we validate the recently published BAVENO VI guidelines for using non-invasive criteria in patients with cACLD to identify patients who are at low risk of clinically significant varices and thus can safely avoid screening endoscopy. We have demonstated that applying such criteria will reduce the number of surveillance endoscopies by about 30%, but could incorrectly classify 2% of patients. Thus adherence to these criteria may delay clinically effective prophylaxis against variceal bleeding with non-selective beta-blockers in a small proportion of patients.

The study included 310 patients. Hepatitis C was the most common aetiology, but with a prevalence of just 55% our cohort reflects a more heterogenous group compared to many of the large studies in this field of predominantly HCV populations (Augustin et al. 2014)(Berzigotti et al. 2013).

The prevalence of all GOV was 23% (18% LRV and 5% HRV). The combination of TE and platelet count with the cut-off values proposed by Baveno VI had a high NPV and low LR-, in contrast to poor PPV and LR+, confirming these markers perform more strongly at ‘ruling out’ rather than ‘ruling in’ HRV, in keeping with the guidelines. A total of 2/15 (13%) cases with HRV had platelets >150 and TE <20kPa and were miss-classified by Baveno VI. Application of the guidelines will have excluded these patients from endoscopic surveillance and delayed the introduction of appropriate primary prophylaxis. However, on

detailed examination of the two cases one had thalassaemia major and also a splenectomy in 1975, which may explain the unusual finding of platelets in the upper limit of normal in the context of cACLD. Careful consideration must therefore be given to co-morbidities which may impact the validity of the proposed platelet cut-off.

Reassuringly only 2/102 (2%) cases meeting BAVENO criteria had HRV, therefore the annual risk to a patient counselled in clinic based on a bleeding rate from varices of 15% per year would be just 0.3% (Garcia-tsao et al. 2007). The guidelines however advise annual assessment of TE and platelet count, followed by endoscopic surveillance of patients who move out of the low risk category. In the miss-classified patients, sequential annual platelet counts were 160000 – 195000 – 188000/μL (HCV, no known haematological co-morbidities) with no further TE data, and 380- 298- 307- 337 (HCV with thalassaemia major and previous splenectomy) with progression in liver stiffness from 16.8kPa to 20kPa on repeat TE four years later. Further longitudinal prospective data will help define the actual risk of bleeding by applying the Baveno VI criteria and if there is an increase compared to current practice due to the inevitable small percentage of high risk varices that will not be captured using non-invasive markers.

Applying the data from our cohort, a reduction in the LSM cut-off to 16.8kPa would have resulted in the inclusion of both the miss-classified cases for endoscopic surveillance. Incorporating this cut-off into the Baveno VI criteria would have correctly identified all patients who could safely avoid screening endoscopy. This would be just below the median LSM 18.4kPa in our cohort and similar to the mean LSM 17.6kPa in a study of compensated cirrhotic patients with no cases of HRV (Augustin et al. 2014), but would result in an additional 27 (13%) endoscopies in our cohort.

The rationale for the Baveno VI guidelines comes from evidence in a number of studies demonstrating that non- invasive investigations such as TE and platelet count show promise in the diagnosis of varices, but generally perform better at excluding rather than

diagnosing high risk varices. A study by Berzigotti et al in compensated cirrhotics showed that TE, in combination with platelet count and spleen size, had a NPV 0.95 and LR- 0.13 compared to PPV 0.55 and LR+ 2.63 when the cut-off was set for a sensitivity of 90%(Berzigotti et al. 2013). Similarly Stefanescu et al showed that TE combined with additional serological and radiological markers produced a NPV 1.0 and LR- 0.1 for high risk oesophageal varices (Stefanescu et al. 2014). More recently Perezzo et al focussed on TE and platelet count as in the Baveno VI guidelines in a prospective assessment 99 HCV cirrhotic patients (80% Child Pugh A, 63% female): 14% had HRV, all of which were appropriately classified by the Baveno VI criteria. Spleen stiffness did not improve the performance of TE and platelet count to identify low risk patients (Perazzo et al. 2015).

Four aspects of our results should be commented on: firstly, these data suggest there is a role for non- invasive markers in identifying patients at low risk of having clinically significant varices who can safely avoid screening endoscopy. Our reported NPV of 0.98 is similar to the NPV of troponin, which is widely implemented to exclude the diagnosis of myocardial infarction (Al-Saleh et al. 2014). This presents an opportunity to reduce the burden of unnecessary endoscopies for patients who often face many invasive investigations through the course of their disease, but the poor PPV and LR+ show these non- invasive tests cannot replace endoscopy in the diagnosis of varices and deciding which patients warrant treatment with primary prophylaxis. Secondly, the guidelines offer single cut-off values that do not account for underlying aetiology. They do acknowledge that the majority of the work in this area has been in chronic hepatitis C, and the value of TE in diagnosing clinically significant portal hypertension in other aetiologies remains to be ascertained. Reassuringly in our small sub group of ALD and NAFLD cases no HRV were missed by the Baveno VI criteria. This is in keeping with some recent studies which have also investigated the use of TE for diagnosing gastroesophageal varices in heterogenous populations(Ding et al. 2015) (Stefanescu et al. 2014). However, further research is needed to validate these non-invasive markers in other aetiologies, particularly NAFLD and ALD.

Thirdly, the data leading to the current guidelines is drawn from populations with variable disease severity and prevalence of varices. The overall prevalence of HRV in our cohort is 5%, and 2% in the cohort meeting the Baveno VI low risk criteria, which is higher than in a study of carefully chosen compensated cirrhotics that found a 0% prevalence of HRV (Augustin et al. 2014), but somewhat lower than in an earlier meta- analysis of TE in detecting large varices that quoted higher prevalence rates ranging from 14.7 to 48% (Shi et al. 2013). We agree with the Baveno VI statement that the guidelines should only be applied to a population with early, well compensated disease with a low pre-test probability of varices and therefore with a low chance of missing cases requiring treatment. Finally, Baveno VI elected to use TE and platelet count alone. Many of the studies on the non-invasive assessment of varices have used additional serological and radiological markers such as spleen stiffness, platelet- spleen ratio, spleen size and Lok score, which can improve the accuracy of diagnosing varices when used in combination with TE (Takuma et al. 2013)(Stefanescu et al. 2014)(Berzigotti et al. 2013). While the results of our study are promising for the simple, pragmatic use of just TE and platelet count, cases will be missed which will have implications, albeit small, on bleeding risk. Most of these additional non-invasive markers are readily available and could be useful in further refining the accuracy of the diagnostic algorithm.

This study has some limitations. The retrospective design brings inherent limitations of bias, which is a particular factor in the high number of cases that did not have an OGD within 12 months of a transient elastography result demonstrating advanced fibrosis. We think this is probably due to a clinical suspicion of mild disease, reflected in a lower median LSM 15.3kPa in the patients not eventually included, compared to 17kPa in the study population ($p<0.001$). Endoscopy was not performed simultaneously with the TE, with a median duration of time between TE and endoscopy of 120 days. However, this is well below the recommended annual surveillance frequency of high- risk patients without varices, and repeating the analysis on only patients endoscoped within 6 months did not

significantly alter the results (Table 2b and 3b). Moreover, using the presence of varices as an endpoint is limited by variable and subjective reporting of their size. However, this is a real world study and initiation of primary prophylaxis is based on the endoscopic evidence of high risk varices given the impractical nature of routinely measuring HVPG. Therefore, identifying non-invasive techniques to identify patients without varices is directly relevant to clinical practice. Finally, we elected to use a relatively conservative cut-off LSM value of 10kPa for our study cohort based on the Baveno VI definition of patients likely to have compensated advanced chronic liver disease. This is below the accepted cut-off value 13.6kPa for cirrhosis in viral hepatitis, the most heavily studied cohort, and may have reduced the prevalence of HRV and elevated the negative predictive value. However, the HRV prevalence of 5% is higher than in other studies of compensated cirrhotics (Augustin et al. 2014). Moreover, other causes of chronic liver disease such as non- alcoholic liver disease are often poorly represented in this field of research, and the LSM criteria for cirrhosis in non- viral aetiologies is less well defined.

Conclusion

Significant progress has been made in the field on non- invasive markers for diagnosing HRV. Our data partly supports the Baveno VI statement that identifying low risk patients who do not require surveillance endoscopy is a realistic goal with the current technologies, which could produce a significant cost saving and beneficially impact on patient experience. However, this data also highlights that a small proportion of cases will be miss-classified and thus be denied proven prophylactic therapies for primary prevention of variceal bleeding. The risk will be minimised by careful assessment for comorbidities that may affect platelet count, and long-term follow-up with annual TE and platelet count to initiate timely endoscopic surveillance in suitable patients. Confirmation by prospective, longitudinal data collection will give further support to these recommendations.

Acknowledgements:

We would like to thank Talay Hakan, Heather Lewis and Louise Campbell for their help in obtaining extensive transient elastography data in the two institutions. This study received no external funding.

References

Al-Saleh, A. et al., 2014. Performance of the high-sensitivity troponin assay in diagnosing acute myocardial infarction: systematic review and meta-analysis. *CMAJ open*, 2(3), pp.E199–207. Available at: http://cmajopen.ca/cgi/doi/10.9778/cmajo.20130074\nhttp://www.ncbi.nlm.nih.gov/pubmed/25295240\nhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC418318.

Augustin, S. et al., 2014. Detection of early portal hypertension with routine data and liver stiffness in patients with asymptomatic liver disease: A prospective study. *Journal of Hepatology*, 60(3), pp.561–569.

Berzigotti, A. et al., 2013. Elastography, Spleen Size, and Platelet Count Identify Portal Hypertension in Patients With Compensated Cirrhosis. *Gastroenterology*, 144(1), pp.102–111.e1. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0016508512014667.

Bureau, C. et al., 2008. Transient elastography accurately predicts presence of significant portal hypertension in patients with chronic liver disease. , (April), pp.1261–1268.

Ding, N.S. et al., 2015. Liver stiffness plus platelet count can be used to exclude high-risk oesophageal varices. , pp.1–6.

EASL, 2015. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. *Journal of Hepatology*, 63, pp.237–264. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0168827815002597.

de Franchis, R., 2015. Expanding consensus in portal hypertension. *Journal of Hepatology*, 63(3), pp.743–752. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0168827815003499.

Garcia-tsao, G. et al., 2007. AASLD PRACTICE GUIDELINES Prevention and Management of Gastroesophageal Varices and Variceal Hemorrhage in Cirrhosis. , pp.922–938.

Groszmann, R.J. et al., 2005. Beta-blockers to prevent gastroesophageal varices in patient with cirrhosis. *New England Journal of Medicine*, 353, pp.2254–2261. Available at: http://discovery.ucl.ac.uk/40547/.

Perazzo, H. et al., 2015. Reply to “Points to be considered when using transient elastography for diagnosis of portal hypertension according to the Baveno’s VI consensus”. *Journal of hepatology*, 63(4), pp.1049–50. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26212027.

Shi, K.-Q. et al., 2013. Transient elastography: a meta-analysis of diagnostic accuracy in evaluation of portal hypertension in chronic liver disease. *Liver international : official journal of the International Association for the Study of the Liver*, 33(1), pp.62–71. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22973991.

Stefanescu, H., Radu, C et al., 2014. Non-invasive ménage à trois for the prediction of high-risk varices: stepwise algorithm using lok score, liver and spleen stiffness. *Liver international : official journal of the International Association for the Study of the Liver*, pp.1–9.

Takuma, Y. et al., 2013. Measurement of spleen stiffness by acoustic radiation force impulse imaging identifies cirrhotic patients with esophageal varices. *Gastroenterology*, 144(1), pp.92–101.e2. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23022955.

Vizzutti, F. et al., 2007. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. *Hepatology*, 45(5), pp.1290–1297. Available at:

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med5&AN=17464971\nhttp://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:med5&rft.g.

Wadhawan, M. et al., 2006. Hepatic venous pressure gradient in cirrhosis: correlation with the size of varices, bleeding, ascites, and child's status. *Digestive diseases and sciences*, 51(12), pp.2264–9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17080245.

Tables

Table 1: Cohort demographics. Data expressed as median values with interquartile range unless indicated. [#] p value comparing HRV to No HRV groups using Mann Whitney test. HRV High Risk Varices; LRV Low Risk Varices; TE Transient Elastography; LSM Liver Stiffness Measurement.

Patient Demographics	Total n=310 (%)	HRV n=15 (5%)	No HRV n=295 (95%)	*p* value[#]
Male (%)	209 (67)	9 (60)	200 (68)	-
Female (%)	101 (33)	6 (40)	95 (32)	-
Age (y)	58 (51, 66))	56 (49, 67)	57 (51, 66)	0.202
Aetiology				
Hepatitis C (%)	169 (55)	11 (73)	158 (54)	-
Hepatitis B/D (%)	24 (8)	0 (0)	24 (8)	-
Alcohol (%)	40 (13)	1 (7)	39 (13)	-
NAFLD (%)	42 (14)	1 (7)	41 (14)	-
Miscellaneous (%)	35 (11)	2 (13)	33 (11)	-
Time (days) between OGD and TE	120 (53, 208)	83 (53, 261)	120 (51, 204)	0.927
Child Pugh Score				
A (%)	275 (89)	13 (87)	262 (89)	-
B (%)	35 (11)	2 (13)	33 (11)	-

MELD Score	7 (6, 9)	8 (7, 12)	7 (6. 9)	0.073
LSM (kPa)[#]	18.4 (13.6, 27.9)	26.0 (17, 71)	18.4 (13.2, 27.7)	**0.015***
Nodules (%)	15 (5)	0 (0)	15 (5)	
Benign	9 (3)	-	9 (3)	
HCC	6 (2)	-	6 (2)	
Laboratory Results				
Platelets (cells x10^3/µL)	147 (101, 198)	133 (59, 197)	147 (102, 199)	0.197
Alanine aminotransferase (U/L)	64 (38, 104)	91 (49, 102)	64 (38, 105)	0.303
Aspartate aminotransferase (U/L)	67 (40, 113)	102 (69, 133)	65 (40, 111)	0.081
Bilirubin (µm/L)	13 (9,18)	21 (14, 23)	12 (9, 17)	**0.006***
Albumin (g/L)	41 (37, 44)	39 (34, 42)	41 (37, 44)	**0.045***
Sodium (mmol/L)	140 (138, 142)	141 (139, 141)	140 (138, 142)	0.375
Creatinine (µmol/L)	73 (64, 86)	74 (62, 81)	73 (64, 87)	0.959
INR	1.1 (1.0, 1.2)	1.1 (1.1, 1.2)	1.1 (1.0, 1.2)	**0.027***
GOV				
None (%)	238 (77)			
LRV	57 (18)			
HRV	15 (5)			
All varices	72 (23)			

Table 2a: Prevalence of all varices and high risk varices in groups generated by the recommended cut-off values from Baveno VI. LSM Liver stiffness measurement.

Variable	Any Varices		High Risk Varices	
	Yes	No	Yes	No

LSM<20kPa (n=167)	23	144	5	162
LSM≥20kPa (n=143)	49	94	10	133
Platelets≤150x10^3/µL (n=159)	50	109	9	150
Platelets>150x10^3/µL (n= 151)	22	129	6	145
Within Baveno VI criteria: LSM<20kPa and Platelets>150x10^3/µL (n=102)	11	91	2	100
Outside Baveno VI criteria: LSM≥20kPa and/or Platelets≤150x10^3/µL(n=208)	61	147	13	195

Table 2b: Prevalence of all varices and high risk varices in groups generated by the recommended cut-off values from Baveno VI. Sub-analysis of population with OGD within 6 months of LSM. LSM: Liver stiffness measurement; OGD: oesophagogastroduodenoscopy.

Variable	**Any Varices**		**High Risk Varices**	
	Yes	No	Yes	No
LSM<20kPa (n=112)	20	92	4	108
LSM≥20kPa (n=107)	35	72	6	101
Platelets≤150x10^3 /µL (n=118)	41	77	8	110
Platelets>150x10^3 /µL (n= 101)	14	87	2	99
Within Baveno VI criteria: LSM<20kPa and Platelets>150x10^3 /µL (n=66)	9	57	1	65
Outside Baveno VI criteria: LSM≥20kPa and/or	46	107	9	144

Platelets≤150x10^3 /µL (n=153)

Table 3a: Performance of each variable for diagnosing high risk varices. LSM liver stiffness measurement; PPV positive predictive value; NPV negative predictive value; LR+ positive likelihood ratio; LR- negative likelihood ratio.

Variable (Cut-off value)	Sensitivity	Specificity	PPV	NPV	LR+	LR-
LSM (20kPa)	0.67	0.55	0.07	0.97	1.48	0.61
Platelets (150x10^3/µL)	0.60	0.49	0.06	0.96	1.18	0.81
Baveno VI criteria [LSM (20kPa) *and* Platelets (150x10^3/µL)]	0.87	0.34	0.06	0.98	1.31	0.39

Table 3b: Performance of each variable for diagnosing high risk varices. Sub-analysis of population with OGD within 6 months of LSM. OGD: oesophagogastroduodenoscopy; LSM: liver stiffness measurement; PPV positive predictive value; NPV negative predictive value; LR+ positive likelihood ratio; LR- negative likelihood ratio.

Variable (Cut-off value)	Sensitivity	Specificity	PPV	NPV	LR+	LR-
LSM (20kPa)	0.60	0.52	0.06	0.94	1.24	0.77
Platelets (150x10^3/µL)	0.80	0.47	0.07	0.98	1.52	0.42
Baveno VI criteria [LSM (20kPa) *and* Platelets	0.90	0.31	0.06	0.98	1.31	0.32

(150x10^3/µL)]

Table 4: The performance of Baveno VI criteria in a sub analysis by aetiology. PPV positive predictive value; NPV negative predictive value; LR+ positive likelihood ratio; LR- negative likelihood ratio; NAFLD Non-alcoholic fatty liver disease; ALD Alcohol- related liver disease

Variable (Cut-off value)	Sensitivity	Specificity	PPV	NPV	LR+	LR-
Viral Hepatitis	0.82	0.28	0.06	0.96	1.13	0.66
NAFLD	1.00	0.46	0.04	1.00	1.86	0.00
ALD	1.00	0.41	0.04	1.00	1.70	0.00
ALD/NAFLD	1.00	0.45	0.04	1.00	1.82	0.00

Figures Legends

Fig. 1: Flow chart of patients evaluated for inclusion in the study
LSM: Liver Stiffness Measurement; OGD oesophagogastroduodenoscopy; LSM liver stiffness measurement; NSBB: pre-existing treatment with non-selective beta blocker;

Fig. 2: Summary prevalence of HRV in the study cohort of low risk and high risk patients as defined by the Baveno VI criteria. HRV: high risk varices; LSM: liver stiffness measurement.

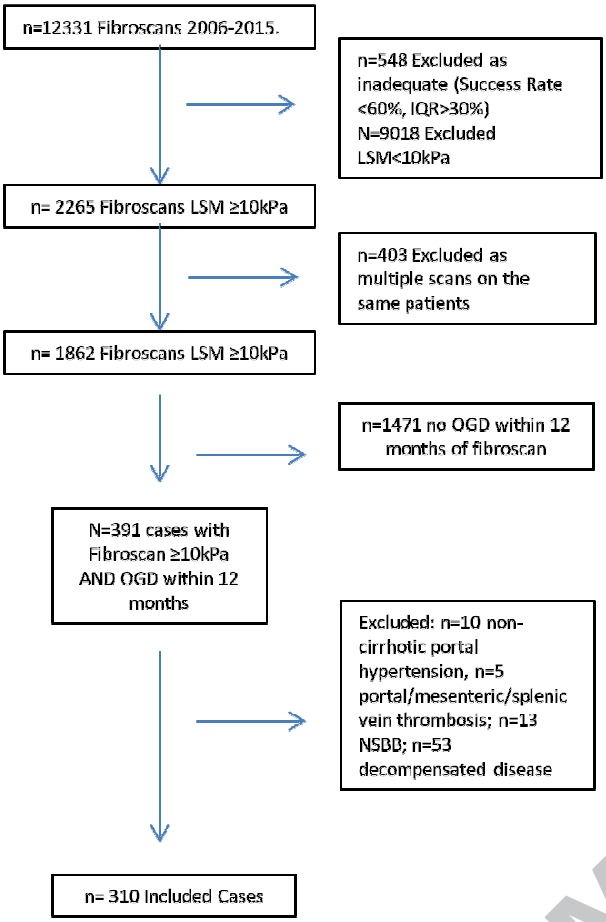


Figure 1

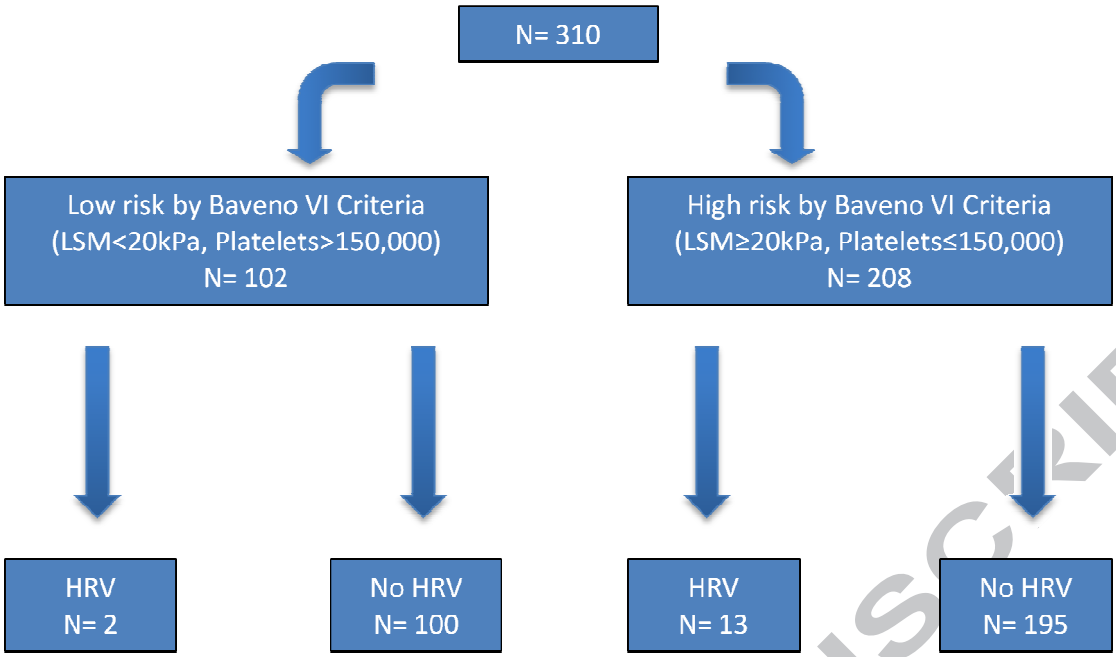
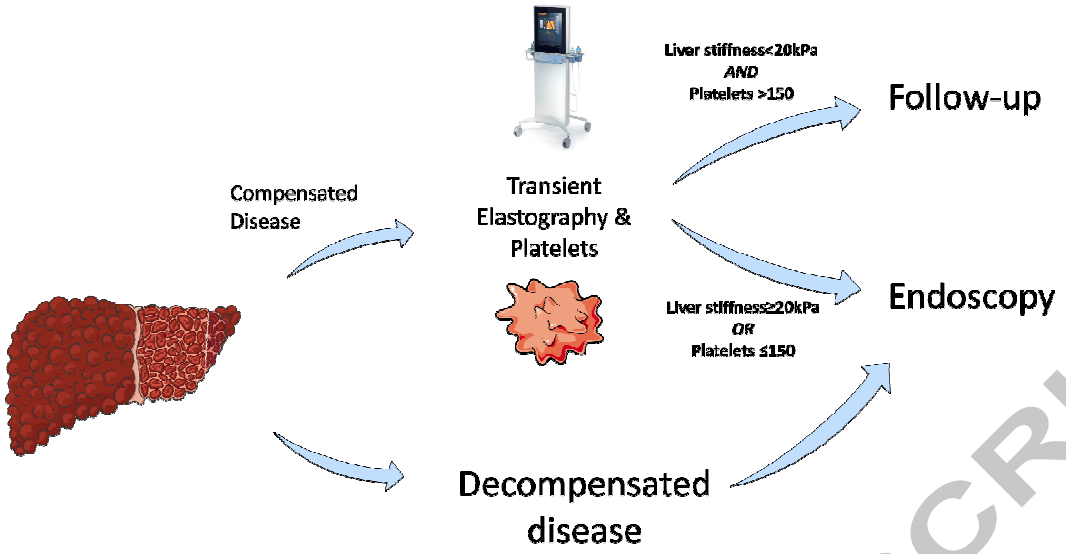


Figure 2



BAVENO VI: CAN WE CONFIDENTLY IDENTIFY LOW RISK CIRRHOTIC PATIENTS NOT REQUIRING ENDOSCOPIC SURVEILLANCE FOR VARICES?