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Risk stratification in acute variceal bleeding: Comparison of the AIMS65 score to established upper gastrointestinal bleeding and liver disease severity risk stratification scoring systems in predicting mortality and rebleeding

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Title: Risk stratification in acute variceal bleeding: a comparison of the AIMS65 score to established upper gastrointestinal bleeding and liver disease severity risk stratification scoring systems in predicting mortality and rebleeding.

Running title: Risk stratification in acute variceal bleeding

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Adrian Swaine: acquisition of data
Gillian Skardoon: study concept and design; acquisition of data
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William Sievert: critical revision of the manuscript
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Abstract:

Objectives: Risk stratification is recommended in all patients with acute variceal bleeding (AVB). It remains unclear whether liver disease severity or upper gastrointestinal bleeding (UGIB) scoring algorithms offer superior predictive ability. We aimed to validate the AIMS65 score as a predictor of mortality in AVB, and to compare AIMS65 with established UGIB and liver disease severity risk stratification scores.

Methods: ICD-10 codes identified patients presenting with AVB to 3 tertiary centres over a 48-month period. Patients were risk stratified using AIMS65, Rockall, pre-endoscopy Rockall, Child-Pugh, Model for Endstage Liver Disease (MELD) and United Kingdom MELD (UKELD) scores. Primary outcomes were inpatient and 6-week mortality and inpatient rebleeding.

Results: Two hundred and twenty three patients were included. Inpatient and 6-week mortality were 13.9% and 15.5% respectively. Prediction of inpatient mortality by AIMS65 (AUROC 0.84) was equivalent to UGIB (Rockall 0.79, pre-Rockall 0.78) and liver risk scores (MELD 0.81, UKELD 0.79, Child-Pugh 0.78). An AIMS65 score ≥3 best defined high- and low-risk groups for inpatient mortality (mortality 37.7% vs. 4.9%). AIMS65 (AUROC 0.62) was equivalent to UGIB risk scores (pre-Rockall 0.64, Rockall 0.70) in predicting inpatient rebleeding and superior to liver risk scores (MELD 0.56, UKELD 0.57, Child Pugh 0.60).

Conclusions: AIMS65 is equivalent to established UGIB and liver disease severity risk stratification scores in predicting mortality and superior to liver scores in predicting rebleeding.

Key words: AIMS65 score; Cirrhosis; Portal hypertension; Upper gastrointestinal bleeding; Variceal bleeding

Full text:

Introduction:

Acute variceal bleeding (AVB) remains a common and life-threatening medical emergency in patients with portal hypertension[1]. Advances in the management of AVB have correlated with significant improvements in inpatient and 30-day mortality rates, from 30%-50% to 11%-20%[2–5] in more recent studies. Despite this, AVB continues to be a leading cause of death in patients with cirrhosis. Multiple factors are responsible for the improvement in patient outcomes, including evolutions in patient management, such as empiric antibiotic usage, coupled with an expanded therapeutic armamentarium, which now incorporates pharmacological, endoscopic and radiological therapies[6]. Comprehensive practice guidelines have also been developed by the American Association for the Study of Liver Diseases (AASLD), British Society of Gastroenterology and Baveno VI consensus conference which detail standards-of-care for managing AVB[7–9].

Recent AASLD practice guidelines emphasise that risk stratification in AVB should be considered essential[7]. It remains unclear, however, whether measures of liver disease severity or UGIB risk stratification algorithms offer superior predictive ability. The severity of a patient's underlying liver disease is traditionally considered one of the strongest predictors of mortality and both the Child-Turcotte-Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores are predictive of outcomes[6,10–12]. Multiple UGIB risk scores have also been developed to predict outcomes in UGIB; the best-validated in AVB is the Rockall score[13], which predicts inpatient mortality[14] (Supplementary Table 1). Limitations of the Rockall score include complexity in calculation (including multiple weighted variables) and the presence of subjective components such as the severity of patient comorbidities. Additionally, as the Rockall score includes endoscopic data it cannot be calculated on presentation. A modified pre-endoscopy or “admission-Rockall” score does facilitate early risk stratification, however its accuracy has been questioned in some studies[15,16].

AIMS65 is a risk stratification score developed by Saltzman *et al*. to predict in-hospital mortality in patients presenting with UGIB[17] (Supplementary Table 1). Multiple retrospective and prospective studies have demonstrated the AIMS65 score to be superior to the Glasgow Blatchford Score (GBS) and pre-endoscopy Rockall scores and equivalent to the Rockall score for predicting in-hospital mortality in cohorts of patients with UGIB from variceal and non-variceal aetiologies[18–21]. A major strength of the AIMS65 score is the simplicity of score calculation; it contains no weighted variables and incorporates laboratory values which are routinely measured in the emergency department (ED). Because the AIMS65 score includes elements of both UGIB and liver disease severity risk scores, we postulated that it may accurately identify patients at high-risk of mortality or early complications following AVB.

Our objectives were to define the clinical outcomes of patients after an episode of AVB in Australian centres using current standards-of-care, to validate the AIMS65 score as a predictor of mortality in patients with AVB, and to compare AIMS65 with established endoscopic (pre-endoscopy Rockall, Rockall) and liver disease severity (Child-Pugh, MELD, UKELD) risk stratification scores as predictors of inpatient mortality and re-bleeding.

Methods:

Patient selection and data collection: International Classification of Diseases, Tenth Revision (ICD-10), diagnosis codes retrospectively identified patients with AVB presenting to three tertiary centres, including one transplant centre, over a 48-month period from 2010 to 2014. Exclusion criteria included incomplete data required for calculation of risk stratification scores or if no variceal bleed was found upon review of the medical records. The Human Research Ethics Committee at Monash Health and Austin Health approved the study as audit activity and the committee provided a waiver for informed consent.

For each patient, manual chart review was used to collect demographic data, medical comorbidities, symptoms on admission (hematemesis, coffee ground vomiting, melena, syncope, lethargy, confusion), aetiology of liver disease, medication use, vital signs, laboratory results, evidence of decompensated liver disease, endoscopy findings, blood transfusion, repeat endoscopy, radiological or surgical intervention and outcomes. Where multiple laboratory tests or vital signs were collected between admission and index endoscopy, the most abnormal values were used.

Consistent with previous studies of the AIMS65 score, altered mental status was defined as a Glasgow Coma Score (GCS) of <14 on presentation or documentation of disorientation, lethargy, stupor or coma by a treating clinician[18]. When calculating the AIMS65 and CTP scores, the serum albumin level prior to intravenous albumin administration was used.

All patients were risk stratified using AIMS65, Rockall, pre-endoscopy Rockall (pre-Rockall), CTP, MELD and United Kingdom MELD (UKELD) scores on the first day of admission prior to index endoscopy. The primary outcomes were inpatient and 6-week mortality and inpatient rebleeding. Secondary outcomes were ICU admission and hospital length-of-stay. Death was determined through hospital medical records and confirmed with a patient's Local Medical Officer if required.

Statistical analysis: The ability of each scoring system to predict the primary and secondary outcomes was assessed by calculating the area under the receiver-operating characteristic curve (AUROC) using SPSS software (Version 24, IBM). AUROCs were compared using the DeLong method. For each risk score, we identified a cut-off point that maximised the sum of sensitivity and specificity in predicting the pre-determined endpoints and patients were stratified into low- or high-risk groups using this cut-off threshold. Fisher's exact test was used to compare low- and high-risk groups. All *p*-values were 2-sided, with a threshold of 0.05 denoting statistical significance. Somer's D statistic was used to compare the predictive accuracy of continuous variables such as length of stay.

Results

Patient characteristics

ICD-10 coding identified 223 patients with AVB. Median age was 56 years (range 18-88) and 78% were male. Cirrhosis was diagnosed in 204 (91%) patients with alcohol (64%) and hepatitis C infection (30%) the most common aetiologies; 23 (10%) had HCC. The median CTP score was 8 (IQR 7-10) with 43 (19%), 113 (51%) and 67 (30%) patients classed as Child-Pugh A, B and C respectively; median MELD was 16 (IQR 12-20). Gastroscopy prior to the index bleed was performed in 168 (75%) patients with 105 (47%) having previous endoscopic variceal band ligation (EVL). A prior AVB was experienced by 65 (29%) patients and 52 (23%) patients were prescribed a non-selective beta blocker on presentation. A form of anticoagulation or anti-platelet medication was taken by 29 (13%) patients at the time of presentation and 112 (50%) were on a proton pump inhibitor. Other patient characteristics are shown in Table 1.

Treatment of AVB and adherence with clinical practice guidelines

All patients were treated with vasoactive therapy (octreotide or terlipressin) and 87% received intravenous antibiotics. The median time to endoscopy was 6 hours (IQR 3-14 hours). Oesophageal and gastric varices were found in 207 and 45 patients respectively; 58 (26%) patients had actively bleeding varices at the time of endoscopy. Details of endoscopic treatment are found in table 2. Haemostasis was achieved in 202 (90.4%) patients following endoscopy. Sengstaken tubes were placed in 32 (14%) patients: 11 at external institutions to facilitate transfer to a study centre; 18 at index endoscopy to facilitate haemostasis, and 3 after index endoscopy due to rebleeding. Red cell transfusion was required in 159 patients (71%) with a median transfusion of 3 units (range 0-24). Seven patients underwent an early transhepatic portosystemic shunt (TIPSS) procedure for failure to gain haemostasis.

Mortality

In-hospital and 6-week mortality were 13.9% and 15.5% respectively. The most common causes of death were complications of decompensated liver disease (18 patients), multi-organ failure (9 patients), sepsis (8 patients) and fulminant or refractory bleeding (8 patients). Median time to inpatient death was 7 days (range 0–45 days). Consistent with previous studies, mortality increased with CTP category with a mortality rate of 2.3%, 8.0% and 31.3% for Child-Pugh A, B and C patients. Twelve-month mortality was 35%.

Performance of risk stratification algorithms

Mortality

AIMS65 (AUROC 0.84) was equivalent to UGIB (Rockall 0.79, pre-Rockall 0.78) and liver risk scores (MELD 0.81, UKELD 0.79 and CTP 0.78) in predicting inpatient mortality (Figure 1, Table 3). Mortality rose with increasing AIMS65 score (Figure 2) and no deaths were recorded in patients with an AIMS65 score of zero. The cut-off threshold that optimally defined low- and high-risk groups for mortality was ≥3 for the AIMS65 score (sensitivity 0.68, specificity 0.80, total 1.48), which gave a positive predictive value, negative predictive value and likelihood ratio of 0.36, 0.94 and 3.4 respectively. Inpatient mortality in the high-risk group was 37.7 % vs 4.9% in the low-risk group ($p <0.001$).

Similarly, in relation to 6-week mortality, AIMS65 (AUROC 0.80) was equivalent to UGIB (Rockall 0.76, pre-Rockall 0.76) and liver risk scores (MELD 0.80, CTP 0.78 and UKELD 0.77). A sub-analysis of patients with oesophageal variceal bleeding only showed no significant difference in the performance of the risk stratification scores.

ICU admission

Ninety-seven (43%) patients required ICU admission with a median stay of 69 (IQR 27–144) hours. The AIMS65 score was equivalent to the Rockall score (AUROC 0.69 vs. 0.62) in predicting ICU admission, while the pre-Rockall score failed to reach statistical significance (AUROC 0.53). In relation to liver disease severity scores, the AIMS65 score was equivalent to the CTP and MELD scores (AUROC 0.69 vs. 0.68 and 0.63 respectively) (Table 3) while the CTP score was superior to UKELD (0.68 vs. 0.61, p=0.019) in predicting ICU admission.

Rebleeding

Inpatient rebleeding was documented in 31 (14%) patients with all risk scores poor predictors of this outcome (table 3). The Rockall (AUROC 0.70), AIMS65 (AUROC 0.63) and pre-Rockall (AUROC 0.64) scores were equivalent in predicting rebleeding (Table 3), however all liver disease severity scores failed to reach statistical significance. An AIMS65 score of ≥2 optimally defined low- and high-risk groups for rebleeding (sensitivity 0.84, specificity 0.43, positive likelihood ratio 1.48), with an inpatient rebleeding rate of 5.7% vs. 19.4% (p=0.02).

Length of Stay

The median LOS was 5 days (IQR 4-9 days) and rose with increasing AIMS65 score (Figure 2). The CTP and AIMS65 scores were superior at predicting hospital LOS with a Somer's D statistic of 0.30 (p<0.001) and 0.26 (p<0.001) respectively. The CTP score was superior to both MELD and UKELD in predicting LOS (Somers' D 0.30 (p<0.001) vs. 0.24 (p<0.001) and 0.16 (p=0.001) respectively). The AIMS65 score was superior to the Rockall score (Somers' D 0.26 (p<0.001) vs. 0.14 (p=0.002)), while the pre-Rockall score failed to reach significance (0.07, p=0.15).

Discussion

Variceal bleeding remains a life-threatening emergency in patients with portal hypertension. The ability to rapidly and accurately assess mortality risk at the bedside should further improve clinical management. We found the AIMS65 score to have equivalent predictive ability to liver disease severity scores, which have consistently been viewed as the strongest and most accurate indicators of mortality following AVB. The AIMS65 score was also equivalent to the best-validated UGIB risk scores in predicting mortality. In addition, the AIMS65 score was superior in predicting hospital LOS and was superior to all liver disease severity scores in predicting in-hospital rebleeding. No patient with an AIMS65 score of 0 died and both mortality and LOS increased with increasing AIMS65 score.

Our study is one of the largest to validate the AIMS65 score as an accurate tool to predict mortality in patients with AVB treated with current standards-of-care. Study inclusion criteria were broad and simple, including all adults with confirmed AVB presenting to three metropolitan tertiary centres in Australia, with a total catchment area of approximately two million people. Study results thus represent real world data and should be widely applicable to other treating centers.

Two recent studies support our findings and have recommended that the AIMS65 score be routinely used in the risk assessment and triage of patients with AVB. Wang *et al*. retrospectively analysed 202 patients with AVB and found the AIMS65 score to be equivalent to MELD-Na and superior to MELD, CTP, Rockall and GBS in predicting 6-week mortality[22]. In addition, Mohammad and Morsy compared the AIMS65 score to liver disease severity scores (MELD, CTP) and ICU scoring systems in 120 patients with AVB. The authors concluded that the AIMS65 score is the best scoring system for independently predicting mortality in cirrhotic patients with AVB[23].

Few studies have examined whether UGIB risk scores can predict mortality and rebleeding in AVB. Indeed, patients with variceal bleeding have been thought to constitute a specific and high-risk group, with outcomes largely dependent on the severity of underlying liver disease[9,24]. Reed *et al*. demonstrated that the GBS was not useful in risk assessing patients with AVB; although it correctly identified patients as being at high-risk for requiring intervention, it was a poor predictor of mortality[25]. Budimar *et al*. found that the AIMS65, GBS and pre-Rockall scores were equivalent in predicting mortality and rebleeding and suggested none were useful for predicting outcomes in AVB because of poor discriminative ability[26]. One limitation of this study was that haemostasis was achieved by endoscopic injection sclerotherapy (EIS) in the majority (79%) of patients. EIS has long been superseded by EVL in the management of AVB and thus the study is not reflective of current standards-of-care. Thanapirom *et al*. found that the GBS, Rockall and pre-Rockall scores were not accurate scores for predicting mortality in AVB. Of note, the mortality and rebleeding rates in this study were significantly lower than most studies analysing AVB (4% and 1.8% respectively) and AUROCs for mortality and need-for-intervention were lower than other published studies in both variceal and non-variceal UGIB. More recently, a retrospective Portuguese study found the AIMS65 score to be superior to both the GBS and Rockall score in predicting inpatient mortality in patients with AVB[27].

Multiple guidelines and consensus statements recommend risk stratification in all patients presenting with UGIB. In routine clinical practice, however, utilisation of risk scores remains poor with variable and discrepant uptake between centres[28]. Risk stratification scores are not routinely used to guide management in AVB, at least in part because all presentations are considered high-risk. For some patients, AVB undoubtedly represents a terminal event that manifests as a result of end-stage liver disease, malignancy, delayed presentation and/or non-compliance with treatment. However, with current standards-of-care nearly 90% of AVB presentations will survive the index bleed and be discharged from hospital. Early risk stratification has the potential to identify a sub-set of patients who remain at high-risk of adverse outcomes despite modern management who could be triaged to receive urgent acute care with the aim of reducing morbidity and mortality.

Our study demonstrates that liver disease severity and UGIB risk scores are accurate and largely equivalent in predicting mortality and rebleeding in AVB. In this setting, the simplicity of the AIMS65 score and its ability to be calculated upon presentation would favour its use in clinical practice. The AIMS65 score shares parameters with the CTP score and therefore it is not surprising that it is equivalent in predicting long-term mortality in AVB. The incorporation of age and systolic blood pressure into the AIMS65 score may increase its ability to predict short-term mortality by identifying older or shocked patients that typically have a poorer prognosis. In addition, unlike liver disease scores, the AIMS65 score can accurately identify patients at high-risk of mortality in both variceal and non-variceal UGIB (using a cut-off score of ≥3). This is an important consideration as AVB may be the first manifestation of chronic liver disease and cirrhotic status may not be known upon presentation. The AIMS65 score is also easily employed by front-line physicians who may have little experience of managing AVB. A recent study by Tang *et al*. concluded that for these reasons the AIMS65 score may be the ideal risk stratification score in patients with UGIB presenting to the ED.[29] The inclusion of altered mental status into the AIMS65 score highlights the importance of this parameter in UGIB, as impaired mental status is a significant contributor to outcomes such as ICU admission, LOS and mortality.

Our study has certain limitations including its retrospective design, meaning all data collection and risk score calculations were ascertained through existing clinical records. Errors were minimised by using a small number of data collectors who entered information into a standardised database. The components of the Rockall score that assess patient comorbidities were more difficult to standardize. To enable consistency and in accordance with previous studies involving AIMS65, we used the definition Blatchford *et al.*[30] used in their original work: the presence of those elements in the medical chart[18,19]. In addition, while we followed established clinical treatment guidelines, outcomes may vary with the availability of experienced endoscopic and critical care capability.

In conclusion, advances in the management of AVB have significantly improved inpatient and 6-week mortality, however long-term prognosis remains poor. AIMS65 is as accurate as established UGIB and liver disease severity risk scores in predicting mortality and rebleeding in patients with AVB. The simplicity of the AIMS65 score and its ability to be calculated on presentation may favour its use in clinical practice. Prospective trials are required to analyse whether early identification of high-risk patients can facilitate improved clinical outcomes.

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Conflict of interests: Nil

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Tables and figures:

Table 1: Patient characteristics

Characteristic	**Number (%)**
Total patients	223
Male	173 (78%)
Cirrhosis diagnosed	204 (91%)
Aetiology of liver disease	
Alcohol	142 (64%)
Hepatitis C	66 (30%)
Hepatitis B	23 (10%)
Non-alcoholic fatty liver disease	15 (7%)
Autoimmune hepatitis	4 (2%)
Primary biliary cholangitis	3 (1%)
Primary sclerosing cholangitis	3 (1%)
Other	30 (13%)

Comorbidities	
Ischaemic heart disease	15 (7%)
Congestive cardiac failure	2 (1%)
Chronic obstructive airways disease	11 (5%)
Cerebrovascular disease	10 (4%)
Diabetes mellitus	62 (28%)
Malignancy (other than HCC)	6 (3%)
Hepatocellular carcinoma	23 (10%)
Chronic renal impairment	9 (4%)
Medications	
Aspirin	20 (9%)
Clopidogrel	1 (0.4%)
Warfarin	4 (2%)
Therapeutic low molecular weight heparin	4 (2%)
Non-steroidal anti-inflammatories	4 (2%)
Proton pump inhibitor	112 (50%)
Histamine-2 receptor antagonist	2 (0.9%)
Non-selective beta blocker	52 (23%)
Rifaxamin	4 (2%)
Lactulose	48 (22%)
Spironolactone	83 (37%)
Furosemide	60 (27%)
Score Components	
Age at admission (years)	56 (48 – 65)
Albumin (g/L)	26 (22 – 30)
International normalised ratio	1.5 (1.3 – 1.8)
Bilirubin (umol/L)	34 (18 – 66)
Creatinine (umol/L)	78 (62 – 108)
Serum sodium (mmol/L)	137 (133 – 139)
Mental state change	52 (23%)
Systolic blood pressure (mmHg)	105 (90 – 121)
Haemoglobin (g/L)	87 (73 – 103)
Heart rate (bpm)	97 (84 – 110)
Urea (mmol/L)	8.5 (5.7 – 13.1)
Syncope	30 (13%)
Ascites on presentation	76 (34%)
Encephalopathy on presentation	34 (15%)

Proportions are presented as percentage. Continuous variables are presented as median (interquartile range)

Table 2: Characteristics and endoscopic treatment of the acute variceal bleeding episode

Presenting symptom	**Number**
Haematemesis	174 (78%)
Coffee ground vomitus	50 (22%)
Melena	118 (53%)
Characteristic	
Oesopahegal varices	207 (93%)
- Median Grade of oesophageal varices	2 (IQR 2-3)
- Median number of variceal columns	3 (IQR 2-4)
Gastric varices	45 (20%)
Ulcer from previous banding	22 (9.9%)
Actively bleeding varices at time of endoscopy	58 (26%)
Treatment	
Variceal ligation (Banding)	176 (79%)
- Median number of bands placed	3 (IQR 2-4)
- Unsuccessful deployment	2 (0.9%)
Variceal obturation of gastric varices with histoacryl and lipiodol	14 (6.3%)
Sengstaken tube placement	31 (14%)
Transjugular portosystemic shunt (TIPSS)	7 (3/1%)

Proportions are presented as percentage. Continuous variables are presented as median (interquartile range)

Figure 1: Receiver-operating characteristic curves (AUROCs) for risk stratification scores as predictors of inpatient mortality.

A. The AIMS65 score compared to liver disease severity risk scores (MELD, Child-Pugh, UKELD)

B. The AIMS65 score compared to upper gastrointestinal bleeding risk scores (Rockall, pre-endoscopy Rockall);

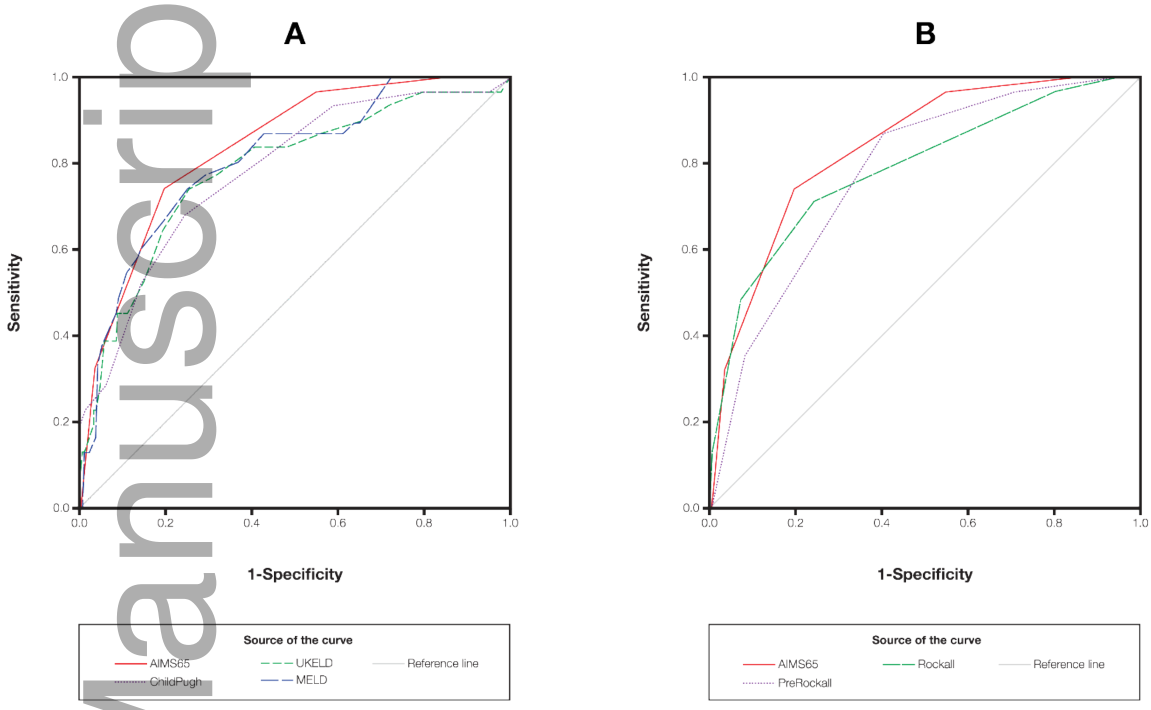
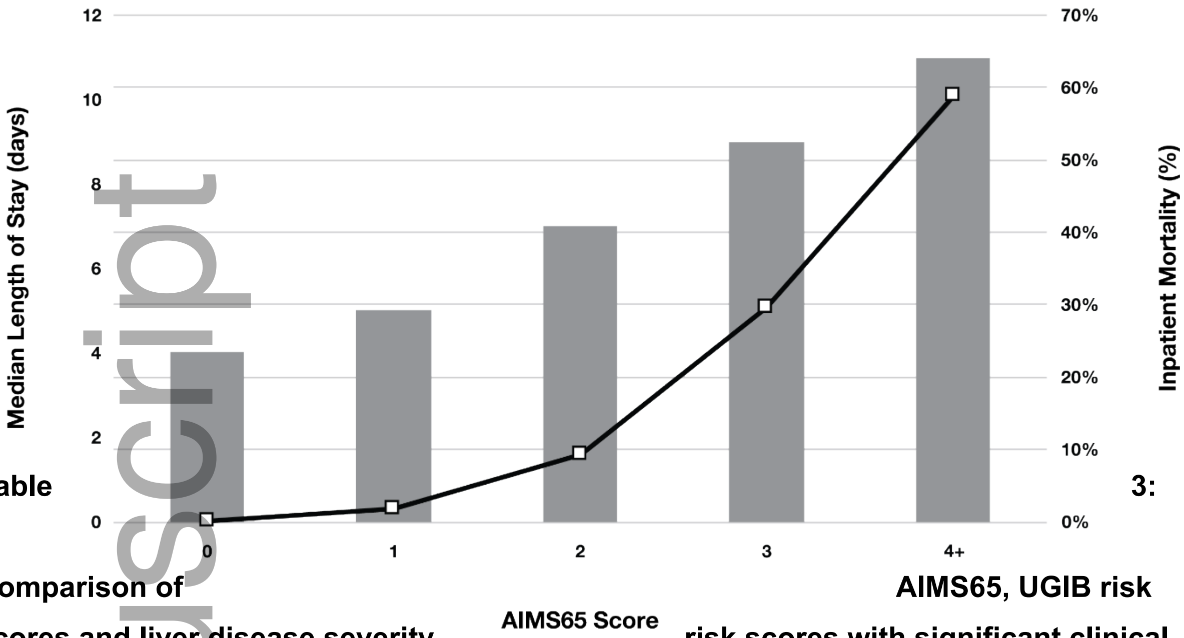


Figure 2: Inpatient mortality rate and length of stay by AIMS65 score. Inpatient mortality and length of stay increased with increasing AIMS65 score



AIMS65 Score	0	1	2	3	4+
Median LOS	4	5	7	9	11
Mortality	0%	1.8%	9.3%	30%	59%

Table 3: Comparison of AIMS65, UGIB risk scores and liver disease severity risk scores with significant clinical endpoints

OUTCOMES	**AIMS65**	**Pre-endoscopy Rockall**	**Full Rockall**	**MELD**	**UKELD**	**Child Pugh**
Inpatient Mortality *AUC (95% CI)*	0.84 (0.77 – 0.91)	0.78 (0.70 – 0.86)	0.79 (0.70 – 0.88)	0.81 (0.73 – 0.89)	0.79 (0.69 – 0.88)	0.78 (0.70 – 0.87)
6-week mortality *AUC (95% CI)*	0.80 (0.72 – 0.88)	0.76 (0.68 – 0.85)	0.76 (0.67 – 0.86)	0.80 (0.72 – 0.88)	0.77 (0.68 – 0.86)	0.78 (0.69 – 0.87)
ICU Admission *AUC (95% CI)*	0.69 (0.62 – 0.75)	0.53* (0.46 – 0.60)	0.62 (0.56 – 0.69)	0.63 (0.57 – 0.70)	0.61 (0.55 – 0.68)	0.68 (0.62 – 0.74)
Transfusion *AUC (95% CI)*	0.70 (0.63 – 0.76)	0.60 (0.53 – 0.67)	0.63 (0.57 – 0.70)	0.63 (0.56 – 0.69)	0.55* (0.48 – 0.62)	0.64 (0.57 – 0.70)
Inpatient Rebleeding *AUC (95% CI)*	0.63 (0.54 – 0.72)	0.64 (0.53 – 0.74)	0.69 (0.59 – 0.80)	0.56* (0.43 – 0.69)	0.57* (0.45 – 0.70)	0.60* (0.48 – 0.72)
Hospital Length of Stay	0.26 (p<0.0005)	0.07* (p=0.19)	0.014 (p=0.004)	0.24 (p<0.0005)	0.16 (p=0.001)	0.30 (p<0.0005)

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* did not reach statistical significance in predicting outcome

Supplementary Table 1: Comparison of the upper gastrointestinal bleeding and liver disease risk stratifications scores

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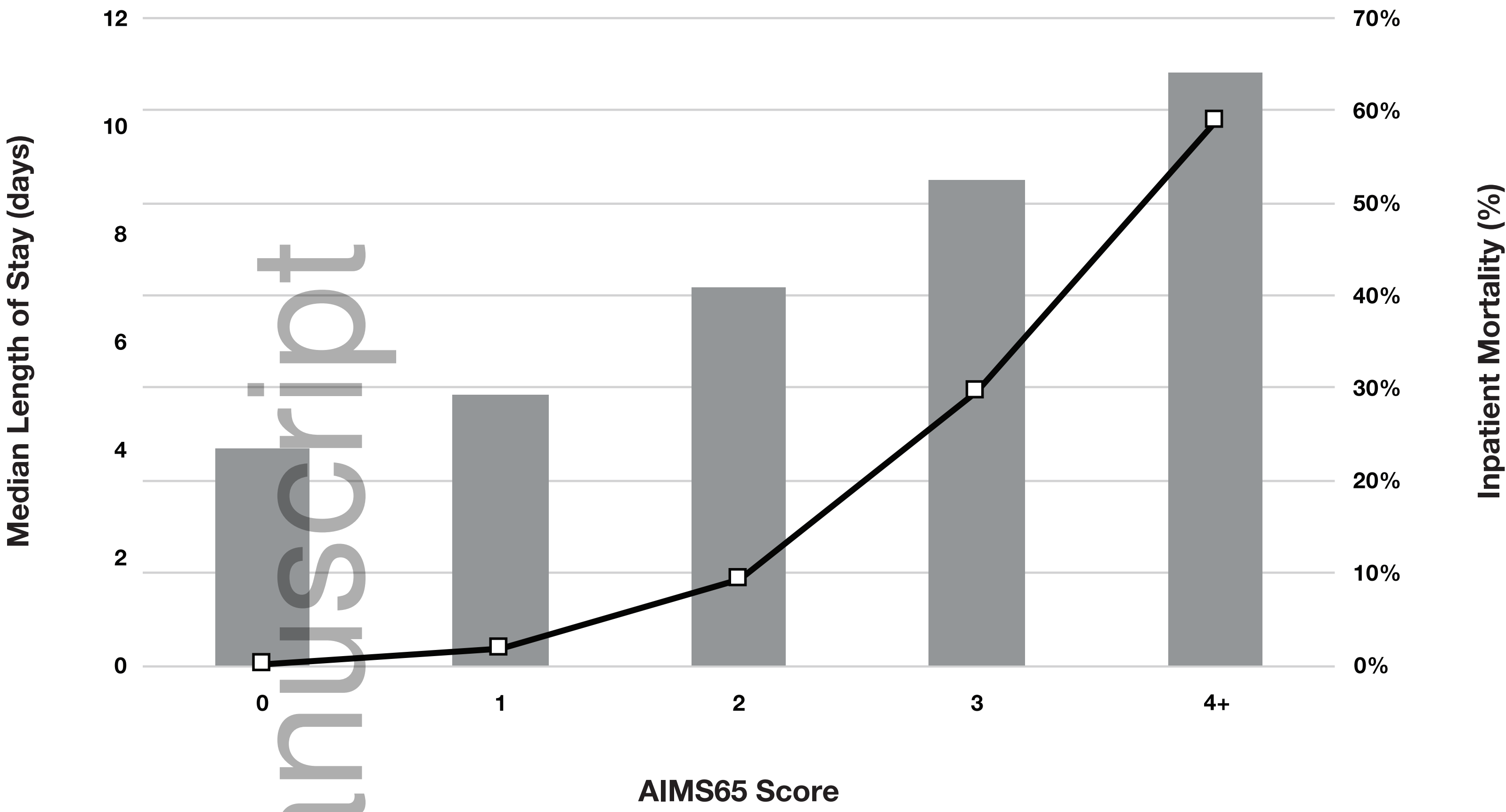

AIMS65 Score	0	1	2	3	4+
Median LOS	4	5	7	9	11
Mortality	0%	1.8%	9.3%	30%	59%

den_13577_f2.eps