Improving transfusion care in acute upper gastrointestinal bleeding

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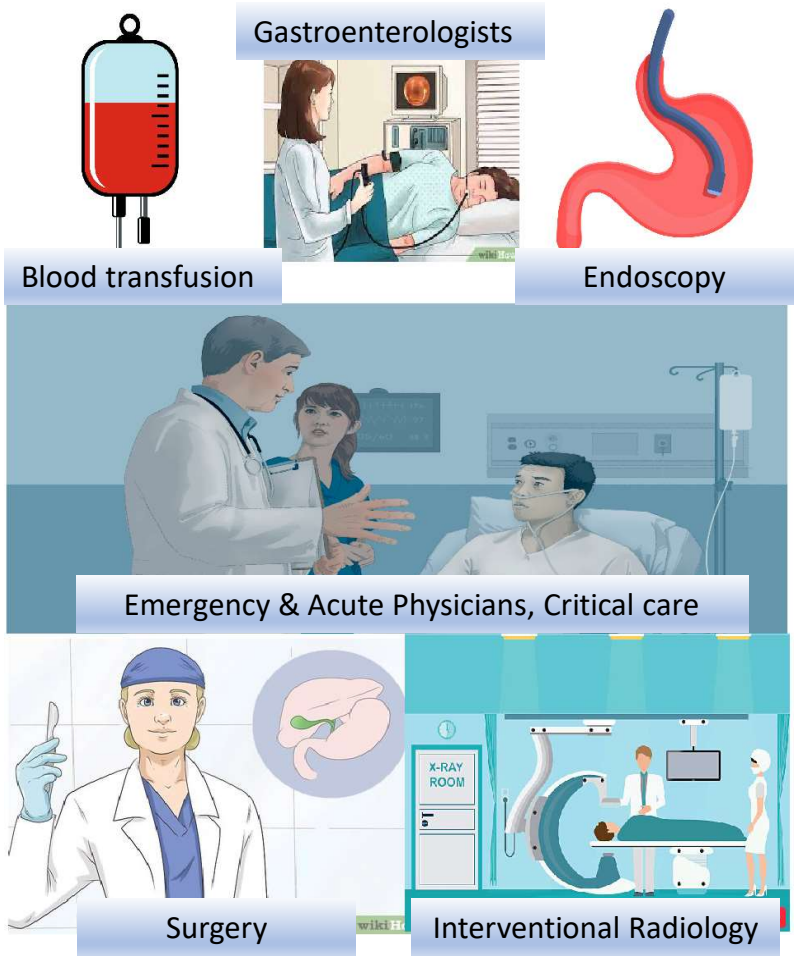
Background

- 50,000 hospital admissions per year across the UK
- Challenging to identify patients at risk of dying or prioritise patients for urgent treatment
- Cost of treatment - over £150 million per year in the UK*
  - Length of stay - £93 million (60%)
  - Endoscopy - £38.5 million (25%)
  - Blood-transfusion - £12.6 million (8%)

*Campbell HE, et al. *BMJ Open.* 2015;**5**:e007230

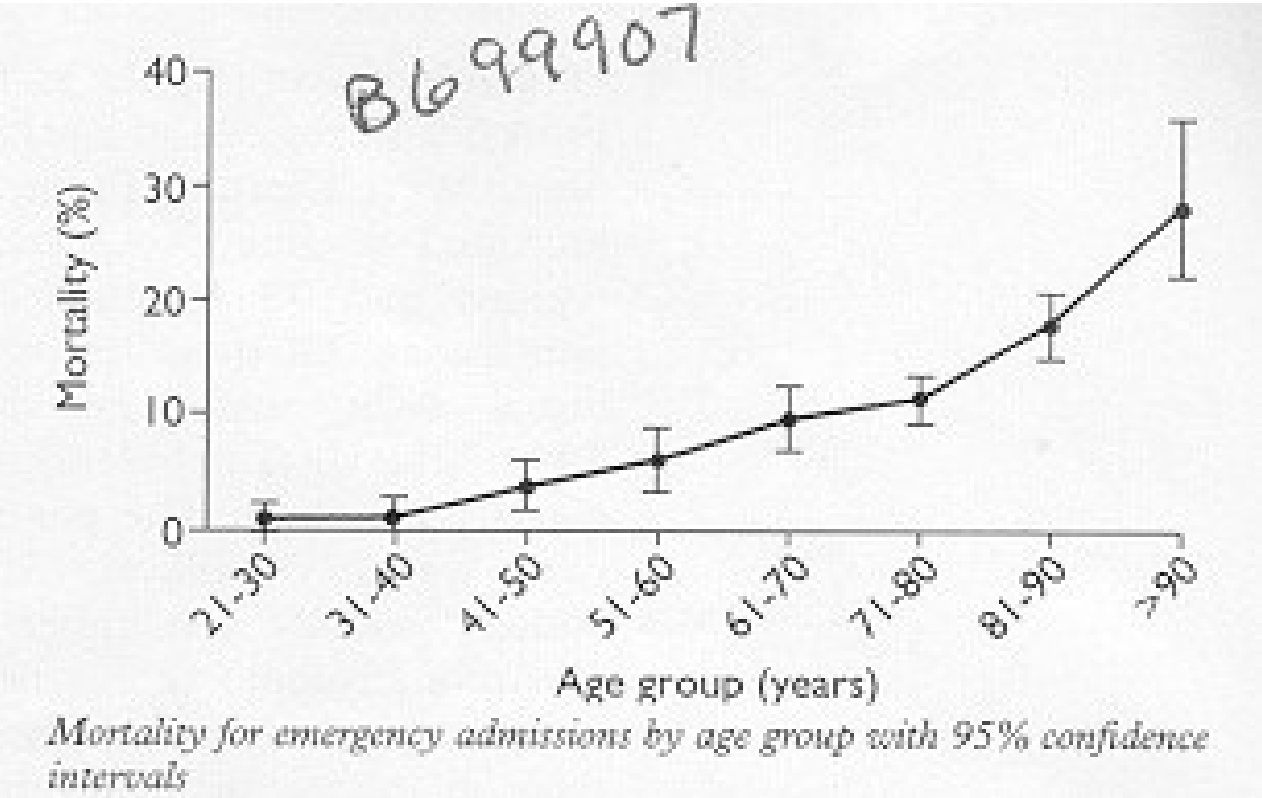
Multi-disciplinary management



- Past
- Present – interim results from UK AUGIB audit 2022
- Future

1993/94 National GI Bleeding Audit

Objective: Describe the current epidemiology of acute upper gastrointestinal haemorrhage
Design: Population based, unselected, multicentre, prospective survey
Setting: 74 hospitals receiving emergency admissions in four health regions in the UK
Subjects: 4185 cases of AUGIB in which patients over 16 years were identified over four months
Outcome measures: Incidence of AUGIB and mortality



Mortality for emergency admissions by age group with 95% confidence intervals

Rockall TA, et al. BMJ 1995;311:222-226

1993/94 National GI Bleeding Re-Audit

Objective: Assess changes in practice and outcome in AUGIB following the feedback of data, and re-emphasis of guidelines following an earlier survey
Design: Prospective, multicentre, audits in two phases 6 months apart
Setting: 45 hospitals in three health regions in the UK
Subjects: 2332 patients in phase 1 and 1625 in phase 2
Results and conclusions: Little demonstrable change in practice and no reduction in mortality

TABLE 5 *Outcomes*

	Phase I	*Phase II*
Days in hospital (acute cases)		
Mean	8.9	8.1
Median	6	5
Days in hospital (low risk: score <2)		
Mean	5.6	5.5
Median	4	4
Surgical intervention for acute bleeding	134/2332 (5.7%)	82/1625 (5.0%)
Crude mortality	13.4% (308/2301)	14.4% (231/1615)
Risk standardised mortality ratio	Reference = 100	0.96 (0.84–1.09)
Surgical mortality	35/134 (26.3%)	17/82 (21.3%)

Further work using these data led to the development of the Rockall scoring system to predict the risk of rebleeding or death

Rockall TA, et al. Gut 1997;41:606-611

Rockall TA, et al. Lancet. 1996 Apr 27;347(9009):1138-40.

Regional audit – West Scotland

Objective: To develop and prospectively validate a risk score to identify a patient's need for clinical intervention

Design: Regional audits and use of logistic regression receiver operating characteristic (ROC) curves to develop score. Validated using data from a second study

Setting: Hospitals in West Scotland

Subjects: Development cohort of 1748 and validation on 197 AUGIB patients

Results and conclusions: validated score identified patients at low or high risk of needing treatment to manage their bleeding. ROC curve area of 0·92 (95% CI 0·88–0·95)

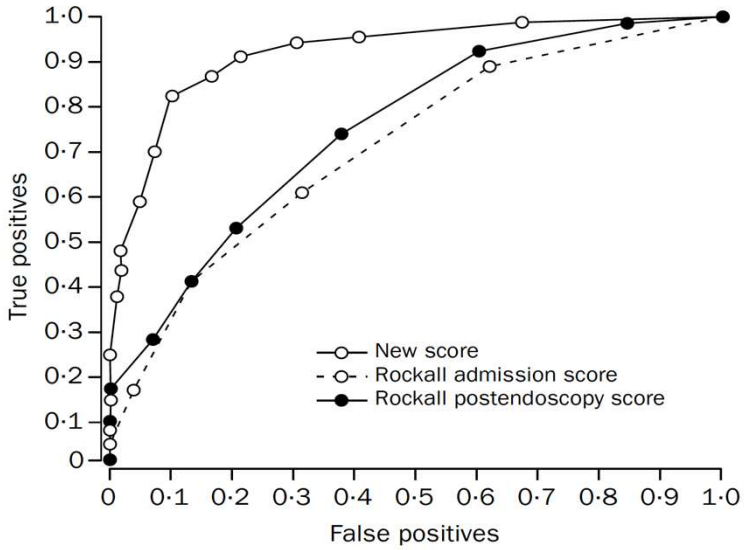


Figure 2: **Receiver operating characteristic curves for new risk score's prediction of need for clinical intervention**
True positives show sensitivity, false positives show specificity.

The new score – Glasgow-Blatchford score established as validated score for predicting need for clinical intervention

Blatchford, et al. Lancet 2000;356:1318-21

Comparative Study > Gut. 2011 Oct;60(10):1327-35. doi: 10.1136/gut.2010.228437.
Epub 2011 Apr 13.

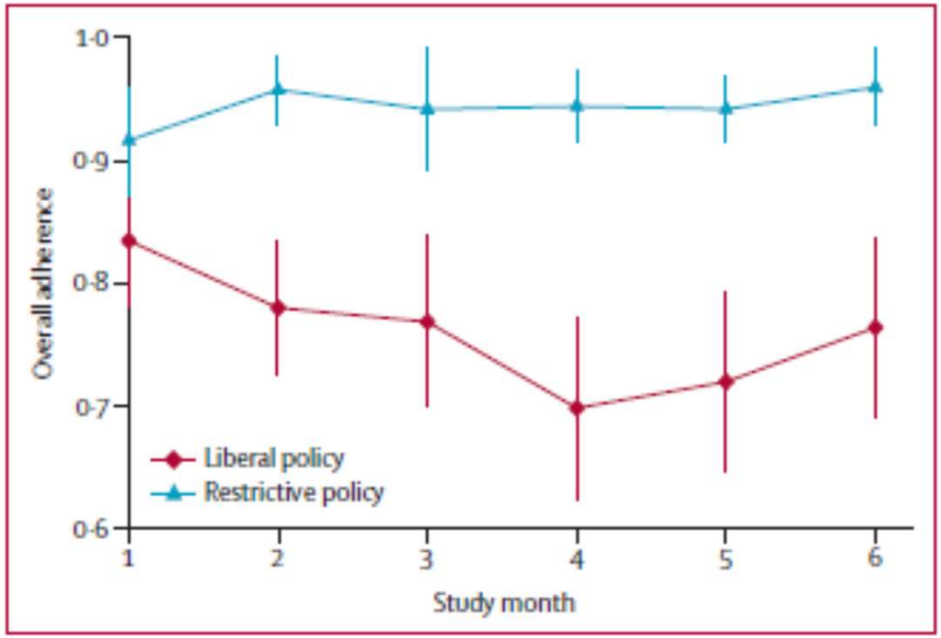
Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses and outcomes in the 2007 UK audit

Sarah A Hearnshaw [1], Richard F A Logan, Derek Lowe, Simon P L Travis, Mike F Murphy, Kelvin R Palmer

Restrictive vs liberal RBC transfusion in AUGIB (TRIGGER): A cluster-randomised feasibility study

Objective: Determine the feasibility of a cluster RCT to study the clinical outcomes of restrictive RBC transfusion in AUGIB
Setting: 6 university hospitals in UK
Design: Hospitals randomised into 2 clusters where AUGIB patients received restrictive (Hb <80g/L) or liberal RBC transfusion (Hb <100g/L)
Subjects: 936 patients with AUGIB
Outcome measures:

1) Feasibility: recruitment rate, protocol adherence etc
2) Clinical: rebleeding and mortality



- Adherence to the restrictive transfusion policy was good
- Adherence in the liberal arm was less good probably due to some **reluctance** to administer transfusions to patients with Hbs <100g/L….practice was already changing

V Jairath et al. Lancet 2015;386:137-144

Restrictive vs liberal RBC transfusion in AUGIB (TRIGGER): A cluster-randomised feasibility study

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Subjects: 936 patients with AUGIB
Outcome measures:

1) Feasibility: recruitment rate, protocol adherence etc
2) Clinical: rebleeding and mortality

- There were no significant differences in clinical outcomes
- But patients in the restrictive arm received less transfusions and had less bleeding and a lower mortality

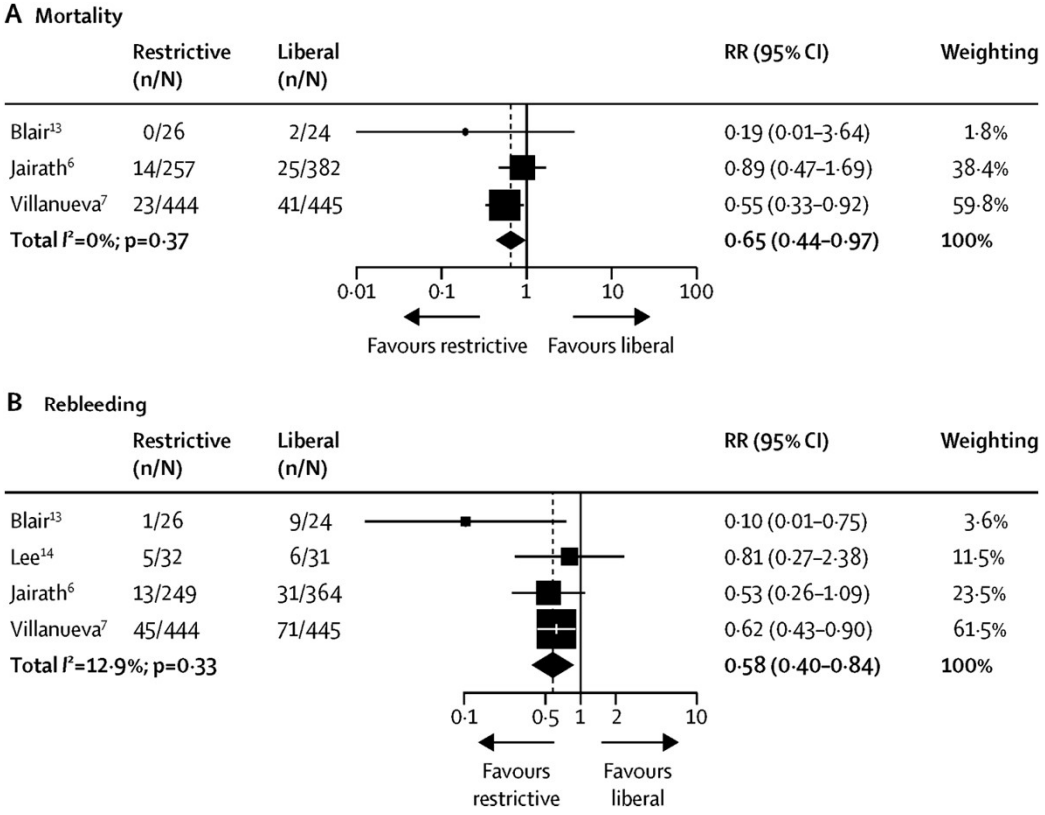
	Liberal policy (n=383)	Restrictive policy (n=257)	Treatment effect*
Further bleeding†			
Day 28	31 (9%)	13 (5%)	−4 (−12 to 5)
Hospital discharge	24 (6%)	9 (4%)	−3 (−13 to 7)
All-cause mortality‡			
Day 28	25 (7%)	14 (5%)	−1 (−8 to 6)

Overall conclusion
Confirmation of the feasibility of a cluster RCT to address the question of restrictive v liberal RBC transfusion in AUGIB

V Jairath et al. Lancet 2015;386:137-144

Restrictive vs liberal RBC transfusion for GIB: meta-analysis of RCTs

- Use of a restrictive transfusion strategy is associated with a reduction in mortality and rebleeding for patients with AUGIB
- Results may not apply to patients with ischaemic heart disease or severe haemorrhage, for whom decisions for transfusion should be based on clinical judgement and individualised risk



Odutayo & Desborough et al. Lancet Gastroenterol Hepatol 2017; 2: 354–60

National Comparative Audit of Blood Transfusion

UK Comparative Audit of Acute Upper Gastrointestinal Bleeding (AUGIB) and the use of Blood 2022

Need for the re-audit

- An appropriate time to repeat a UK wide audit of AUGIB
  - Assess improvements : resource availability, clinical assessment, management, transfusion practice and patient outcomes

- Data will be used to clarify areas of ongoing clinical uncertainty
  - Optimal risk assessment scores: low-risk and mortality predictions
  - Optimal timing of interventions, relationships between out of hours presentation and outcomes

- Improve patient blood management (PBM)
  - Individualising a transfusion plan at presentation: AUGIB often have multiple co-morbidities and varying aetiology for the cause of bleeding
  - Optimal timing of transfusion to streamline resource allocation

- All NHS Trusts in England, Northern Ireland, Wales and Scotland invited to participate in the audit

- Prospectively identified consecutive patients with AUGIB from **3rd May-2nd July 2022** included for the audit

Case Identification

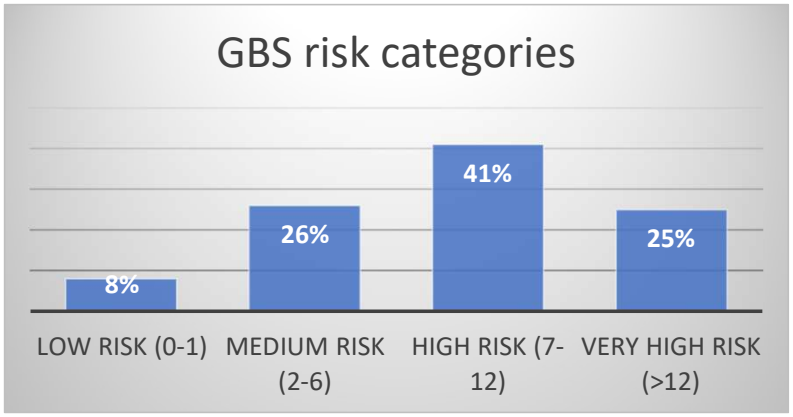
- All cases of AUGIB, between **3rd May until 2nd July 2022**
  - Resulting in a presentation to hospital or developed whilst patients were already hospitalised for another reason
  - Patients did not need to have had a blood transfusion/endoscopy to be eligible

- Inclusion criteria
  - Patients aged ≥ 16, presented to emergency department or admitted to an adult medical/surgical ward
  - Suspected or confirmed AUGIB *(melaena, haematemesis, shock / syncope, coffee ground vomiting)*

Audit tool

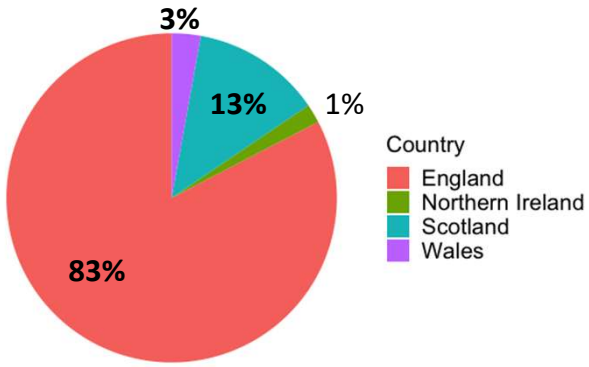
- Audit lead decides whether true case and eligible for inclusion
- Online + Paper forms for data entry
- Data collected from patient's case notes & hospital IT systems
- 35-40 mins per case

Demographics	**Age, gender, ethnicity.**
Clinical history	**Admission date, time, clinical area, and admitting team. Referral patterns (e.g. to Gastroenterology / Surgery/ critical care), past medical history, signs and symptoms at presentation, observations at time of presentation for the clinical episode.**
Laboratory tests	**Results of blood tests performed for the clinical episode.**
Medications	**Details of specific medications administered with dose and duration.**
Interventions	**Details of interventions (endoscopy, transfusion, surgery, interventional radiology) with information on the time of intervention and outcomes.**
Clinical outcomes	**Details on clinical outcomes including final diagnosis, safe discharge, in-patient deaths and cause of death, need for a repeat procedure etc.**



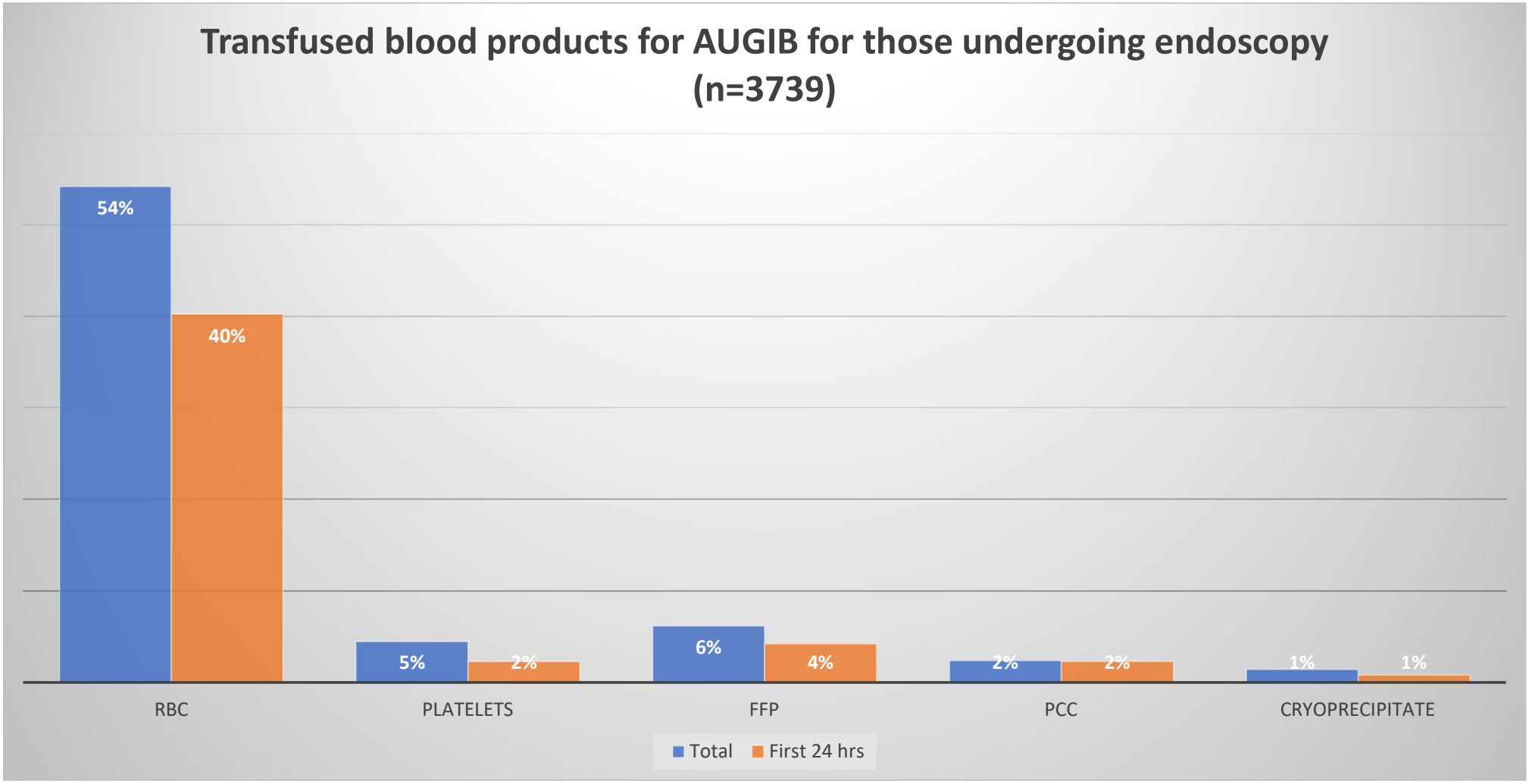
Total cases from 148 hospitals across UK
4528

Total inpatient endoscopy
3739

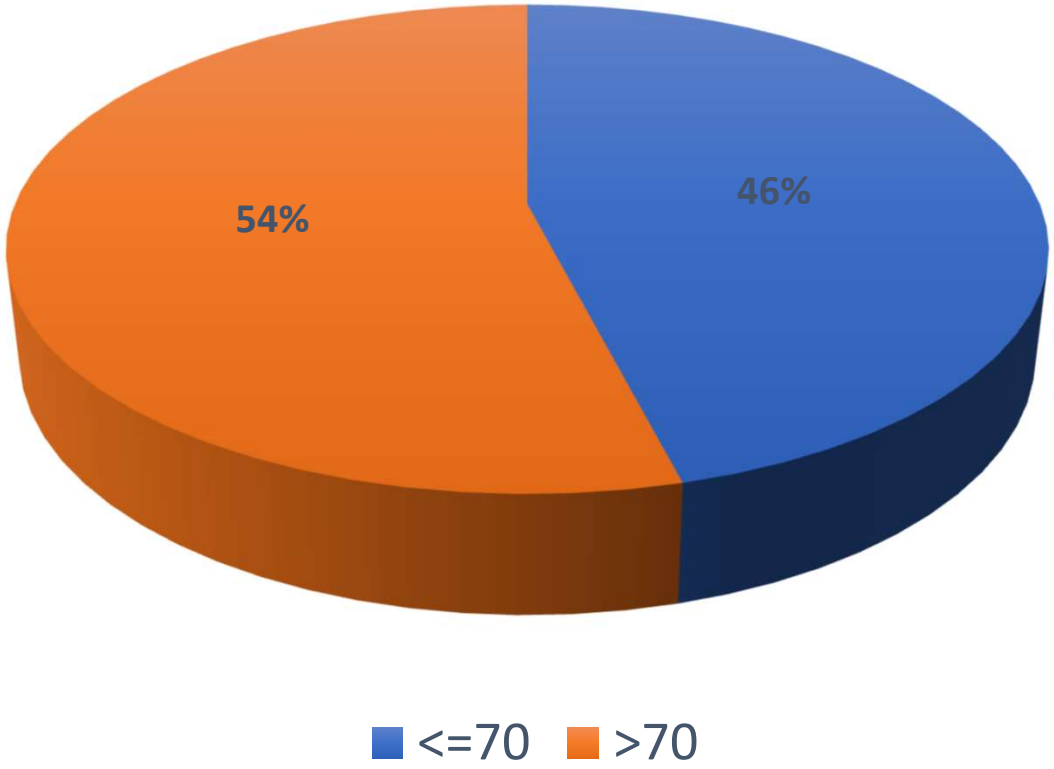


	2007 (n=6750)	2022 (n=4528, interim results of first patients)
Median age	68 yr (IQR 49-81)	69 yr (IQR 54-81)
Any comorbidity	50%	66%
Medications		
NSAID	11%	7%
Antiplatelets	33%	21%
Anticoagulants	13%	31%
Other		
Alcohol excess	26%	30%
Chronic Liver Disease	9%	16%

	2007 (n=6750)	2022 (n=4528, interim results of first patients)
Inpatient endoscopy	74%	83%
PUD	36%	30%
Variceal bleed	11%	10%
Use of endoscopic therapy	24%	27%
Further bleeding after index endoscopy	13%	9%
Surgery	1.9%	0.8%
IR	1.2%	2.5%
Transfusion ≥1 unit		
PRC	43%	49%
Platelets	2.8%	4%
FFP	7%	5%
Median LOS	5 days (IQR 2-12)	5 days (IQR 3-10)
In-hospital mortality	10%	8.8%

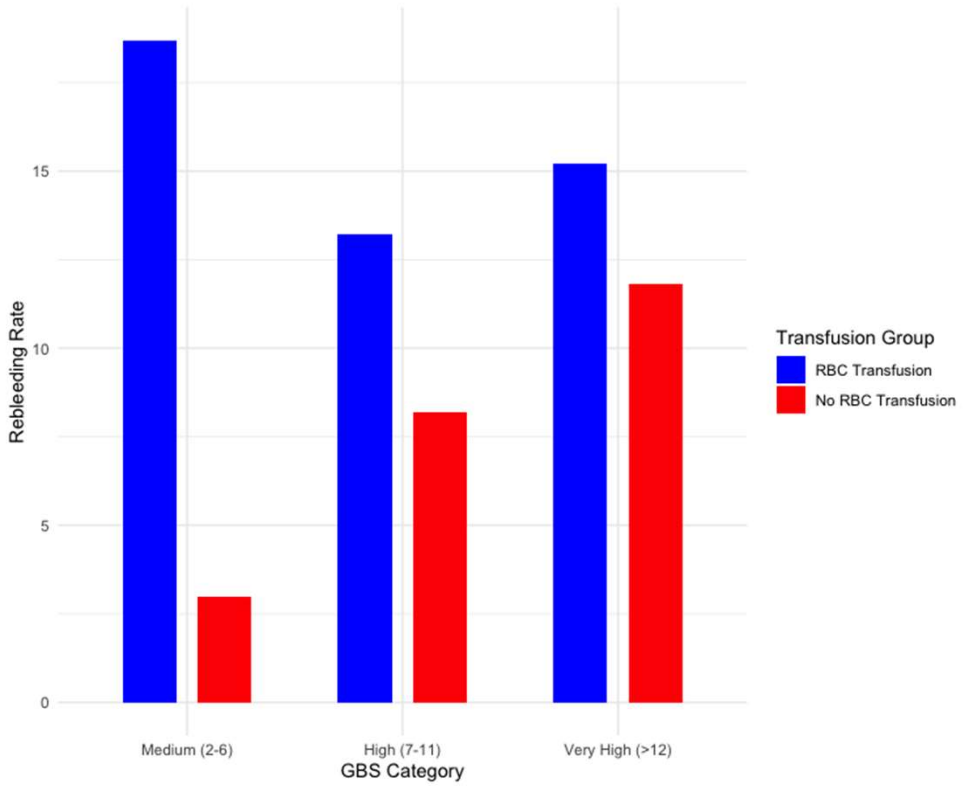

Transfused blood products for AUGIB for those undergoing endoscopy (n=3739)
54%
40%
5%
2%
6%
4%
2%
2%
1%
1%
RBC
PLATELETS
FFP
PCC
CRYOPRECIPITATE
Total
First 24 hrs

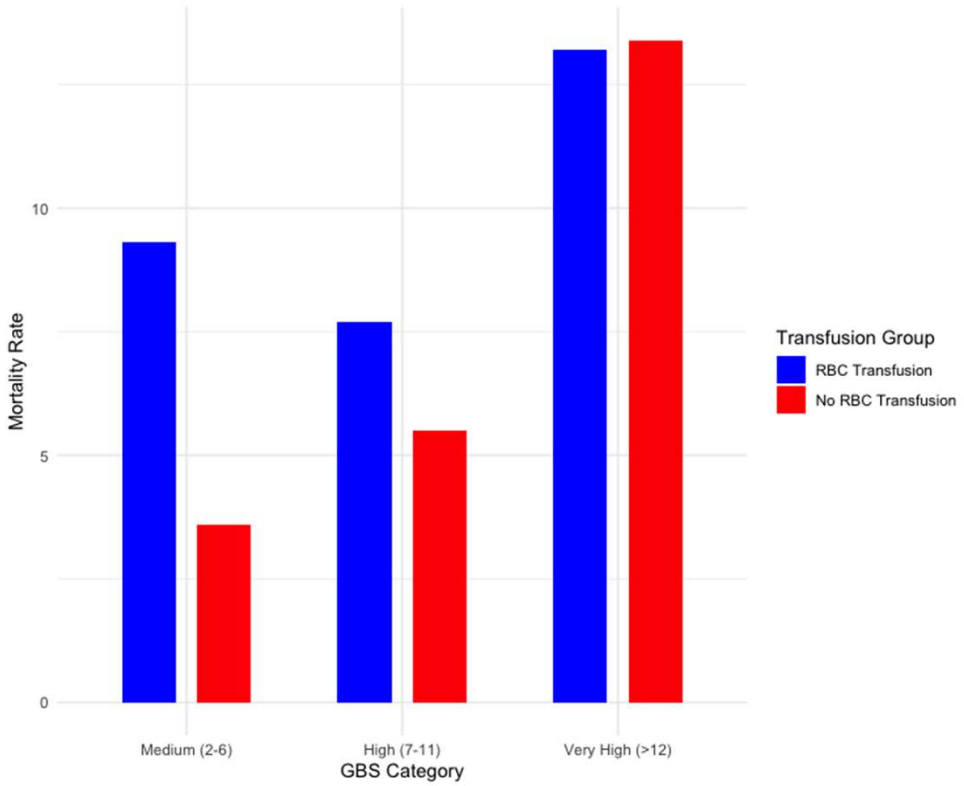
Early RBC transfusion based on initial Hb category



Initial Hb category	Rebleeding			Mortality		
	Early RBC	No early RBC	p-value	Early RBC	No early RBC	p-value
≤70 g/L	15%	14.6%	0.9	10%	9.5%	0.5
>70 g/L	13.4%	5.9%	<0.05	10.4%	5.4%	<0.05

After adjusting for the Glasgow-Blatchford score and initial haemoglobin levels, early transfusion was independently associated with a 56% increased risk of re-bleeding (odds ratio 1.56, 95% CI 1.18–2.08) and a 42% increased risk of mortality (odds ratio 1.42, 95% CI 1.04–1.93).





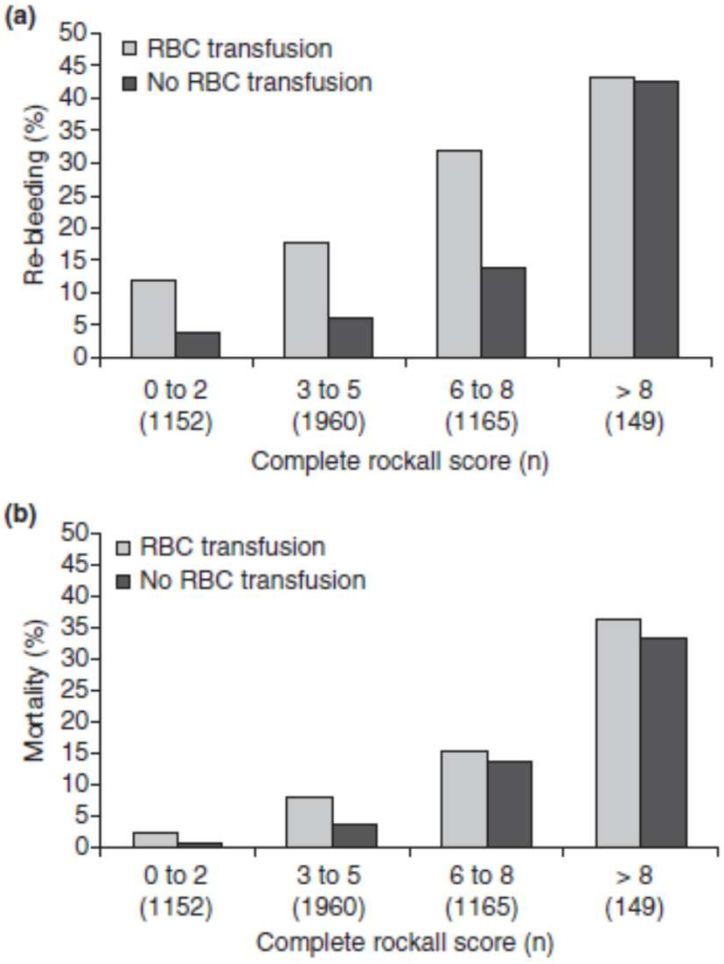
Re-bleeding and mortality by GBS categories in those receiving early RBC transfusion and those not receiving early RBC transfusion.

2007 National GI Bleeding Audit

Objective: To examine the relationship between early RBC transfusion, re-bleeding and mortality following AUGIB
Design: Multicentre, prospective
Setting: 212 UK hospitals receiving emergency admissions
Subjects: 4441 cases of AUGIB

Adjusting for Rockall score and initial Hb, early transfusion was associated with:-

- two- fold increased risk of re-bleeding (OR 2.26, 95% CI 1.76-2.90)
- 28% increase in mortality (OR 1.28, 95% CI 0.94-1.74)

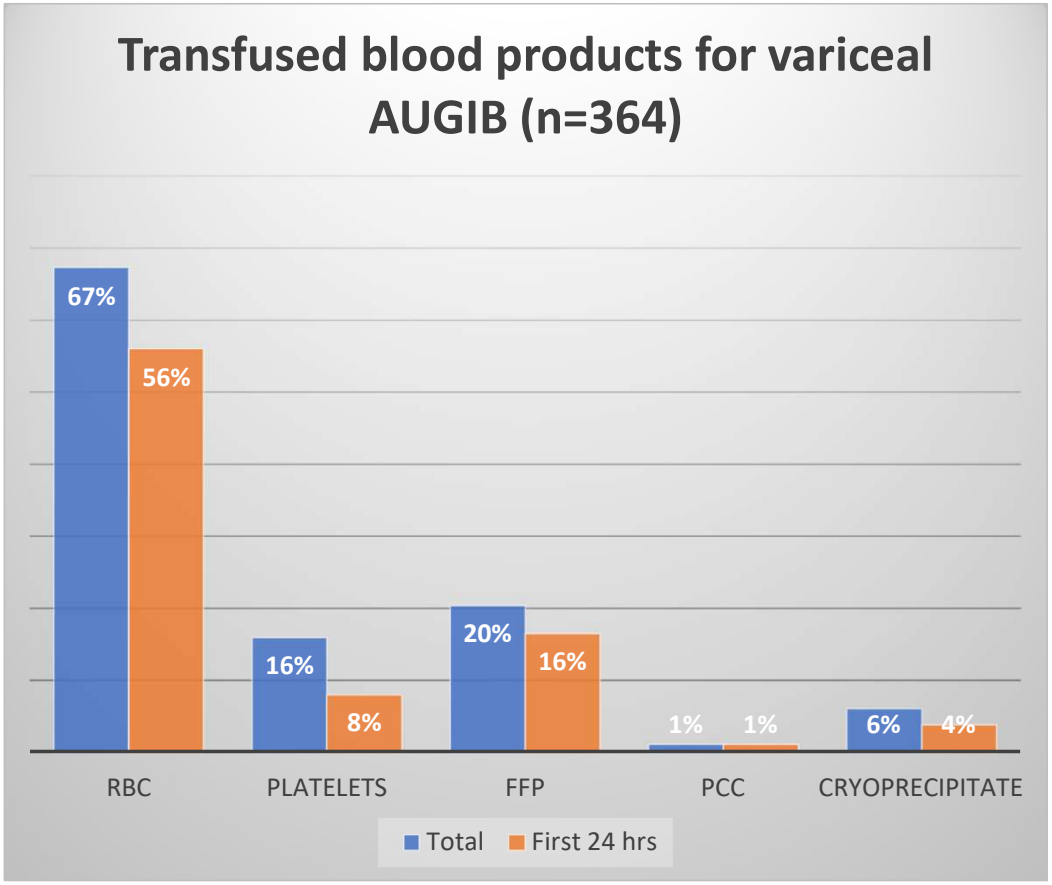


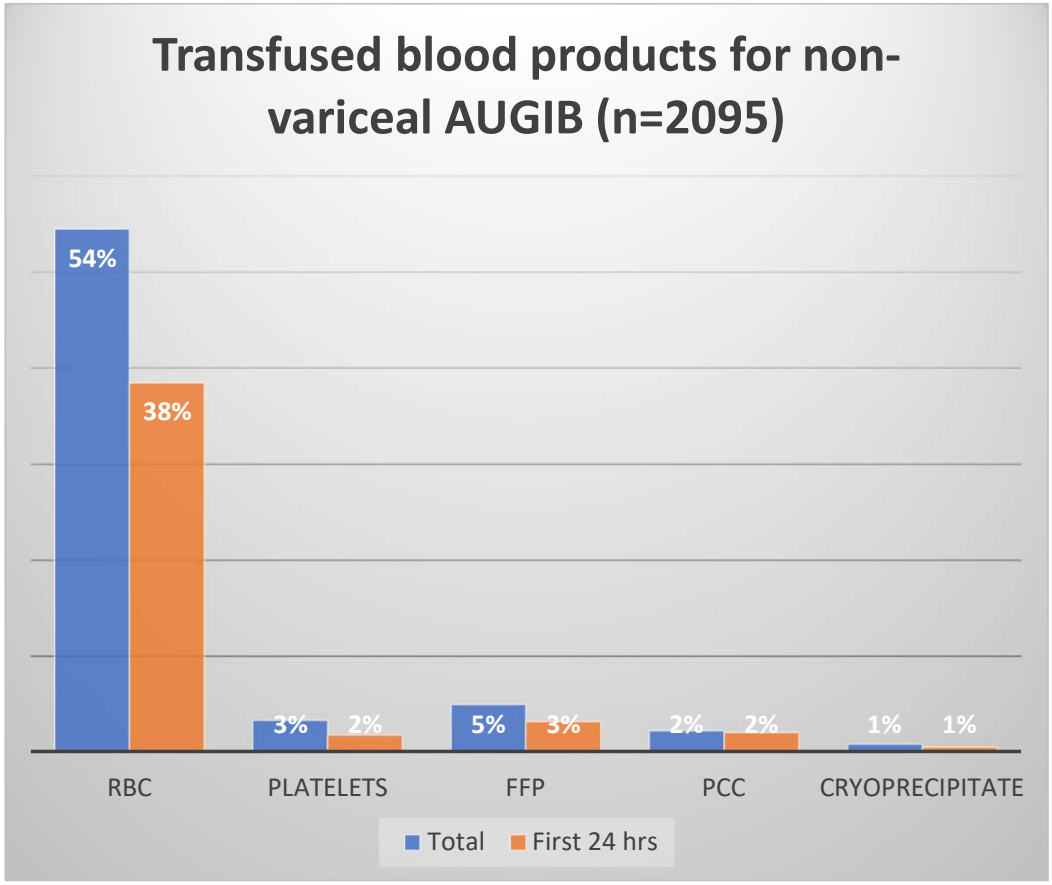
Re-bleeding and Rockall score in patients receiving and not receiving early transfusion

Mortality and Rockall score in patients receiving and not receiving early transfusion

Hearnshaw et al. Aliment Pharmacol Ther 2010; 32: 215–224

Transfused blood products for variceal and non-variceal AUGIB





Outcome	Variceal (n=364)	Non-variceal (n=2095)	p- value
Median age	58 (IQR 49-69)	69 (IQR 55-80)	<0.05
Transfer to HDU or ITU	18%	6%	<0.05
Endoscopy outcomes			
Stigmata of recent bleed	72%	38%	<0.05
Endotherapy	77%	33%	<0.05
Further bleeding after index endoscopy	17%	10%	<0.05
IR	4%	2.5%	0.1
Surgery	0.2%	1.2%	0.08
Transfusion >1 unit			
Packed red cells	67%	54%	<0.05
Fresh frozen plasma	20%	5%	<0.05
Platelets	16%	3%	<0.05
Median LOS	7 days (IQR 4-11)	5 days (IQR 3-10)	<0.05
In-hospital mortality	12.6%	7.4%	<0.05

RBC transfusion for variceal AUGIB

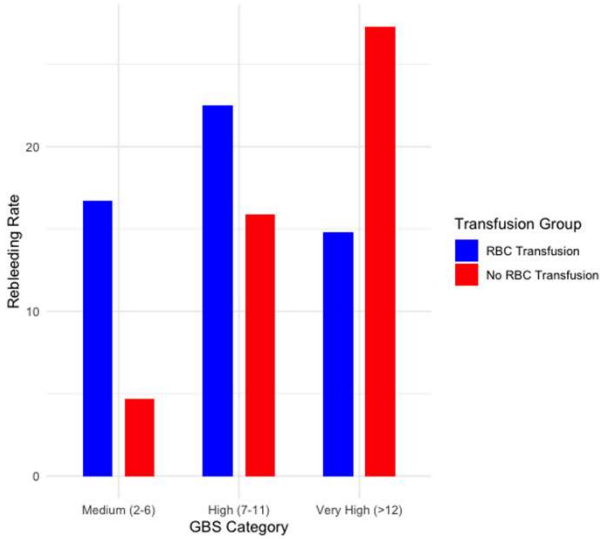
Initial Hb category	**Rebleeding**			**Mortality**		
	Early RBC	No early RBC	p-value	Early RBC	No early RBC	p-value
≤70 g/L	16%	10%	0.6	11.1%	10%	0.9
>70 g/L	19.3%	15.8%	0.4	13.4%	13%	0.9

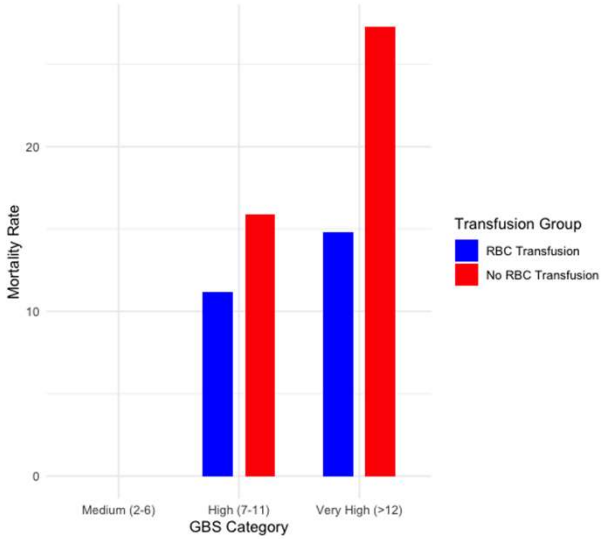
After adjusting for the Glasgow-Blatchford score and initial haemoglobin levels, early transfusion was independently associated with a 5% increased risk of re-bleeding (odds ratio 1.05, 95% CI 0.54–2.06) and a 26% reduced risk of mortality (odds ratio 0.74, 95% CI 0.35–1.55).

RBC transfusion for non-variceal AUGIB

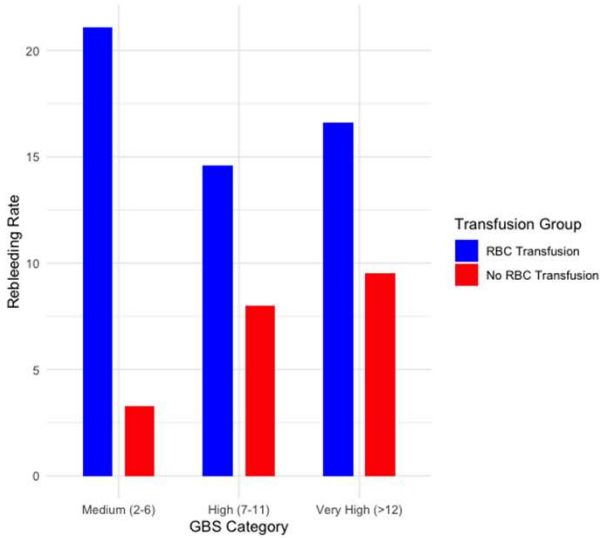
Initial Hb category	**Rebleeding**			**Mortality**		
	Early RBC	No early RBC	p-value	Early RBC	No early RBC	p-value
≤70 g/L	17%	14%	0.5	11.5%	8.3%	0.4
>70 g/L	14%	5.7%	<0.05	9.4%	5.3%	<0.05

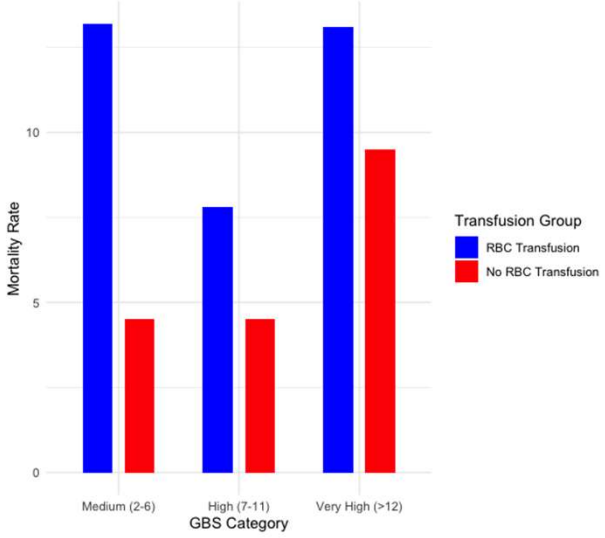
After adjusting for the Glasgow-Blatchford score and initial haemoglobin levels, early transfusion was independently associated with an 80% increased risk of re-bleeding (odds ratio 1.8, 95% CI 1.25–2.64) and a 58% increased risk of mortality (odds ratio 1.58, 95% CI 1.05–2.39).





Variceal Bleed





Non- Variceal Bleed

Re-bleeding and mortality by GBS categories in those receiving early RBC transfusion and those not receiving early RBC transfusion with **variceal and non-variceal bleeds**.

Timeline in management strategies for AUGIB

Rockall Score (1996), Glasgow-Blatchford score (2000) from regional UK audits

2012 NICE guidelines on AUGIB

CHROME statement - services for AUGIB

2015 NCEPOD Report

2020 BSG led multi-society care bundle for AUGIB

What next?

2007 UK AUGIB audit

Deficiencies in resource availability and management strategies

2015-2021: National and International guidelines on management of AUGIB

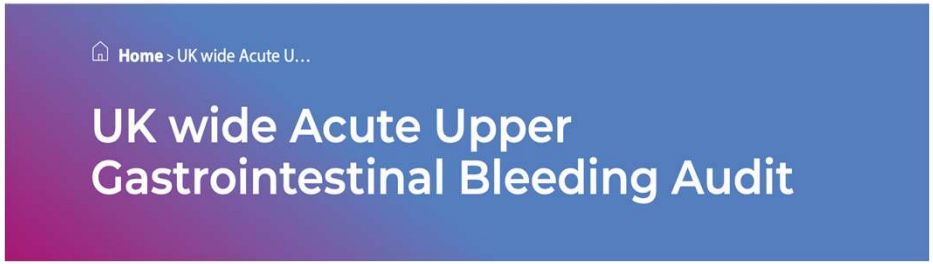
2022 – UK AUGIB audit

Assess changes and impact on management on AUGIB across the UK

BRITISH SOCIETY OF GASTROENTEROLOGY

Royal College of Physicians

NHS Blood and Transplant



Rockall TA. *Gut 1996*; Blatchford O. *Lancet 2000*; Hearnshaw SA. *Gut 2011* ; Tripathi D. *Gut 2015*; Gralnek IM. *Endoscopy 2021*; Siau K, et al. *Frontline Gastroenterology 2020*.

Discriminative ability of evaluated scoring systems

Score	Derivation population	Main predicted outcome	Outcome definition
Rockall Score	All AUGIB, UK	Mortality	In-hospital death
Glasgow-Blatchford Score (GBS)	All AUGIB, UK	Need for treatment	RBC transfusion, intervention to control bleeding, re-bleeding or death
AIMS 65	All AUGIB, USA	Mortality	In-hospital death
PNED	All AUGIB, Italy	Mortality	In-hospital death
CANUKA	All AUGIB, Canada, UK, Australia	Lack of poor outcome	No transfusion, re-bleeding, therapeutic endoscopy, interventional radiology or surgery, or death
ABC	AUGIB and LGIB, Multi-centre	Mortality	In-hospital death in both UGIB and LGIB

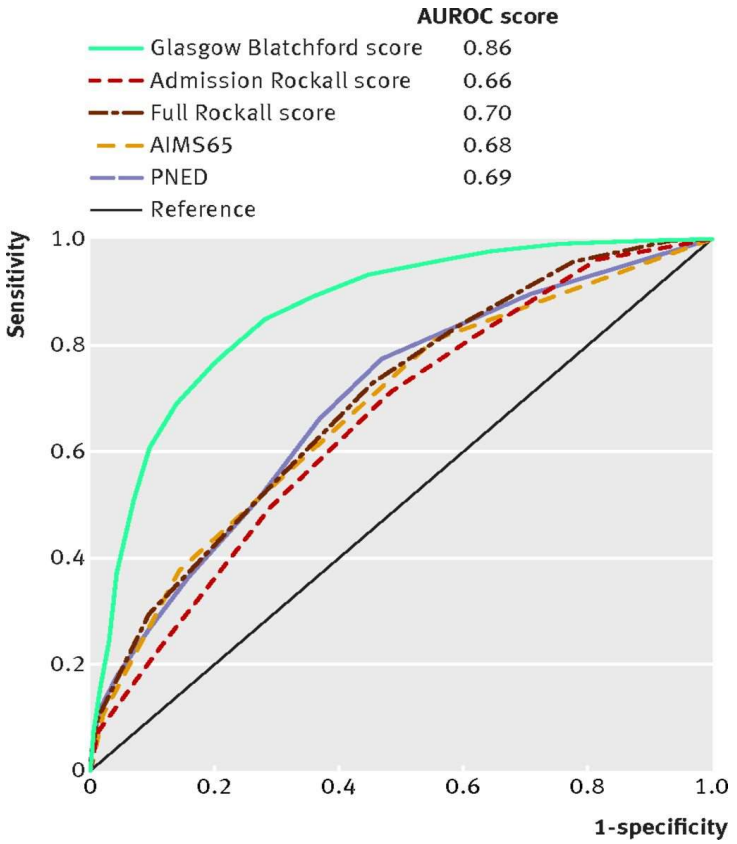


Fig: Comparisons of scores in prediction of need for any intervention (transfusion, endoscopic treatment, interventional radiology or surgery) or 30 day mortality (n=1704).

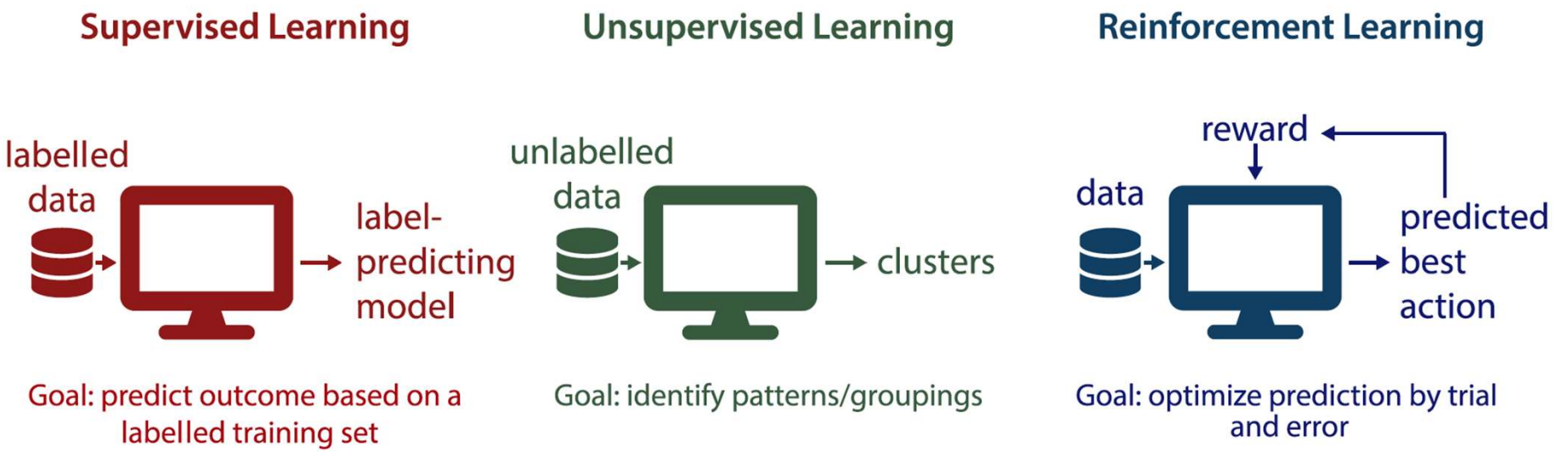
Adrian J Stanley et al. BMJ 2017;356:bmj.i6432

Outcome by scoring system	AUROC (95% CI)
Intervention or death:	
Glasgow Blatchford	0.89 (0.87 to 0.90)
AIMS65	0.70 (0.68 to 0.72)
Admission Rockall	0.69 (0.67 to 0.71)
Full Rockall	0.69 (0.67 to 0.71)
PNED	0.71 (0.70 to 0.73)
Need for endoscopic treatment:	
Glasgow Blatchford	0.75 (0.73 to 0.77)
AIMS65	0.63 (0.60 to 0.65)
Admission Rockall	0.61 (0.59 to 0.64)
Rebleeding:	
Glasgow Blatchford	0.70 (0.66 to 0.74)
AIMS65	0.62 (0.57 to 0.66)
Admission Rockall	0.62 (0.57 to 0.66)
Full Rockall	0.63 (0.58 to 0.68)
PNED	0.85 (0.83 to 0.88)
Mortality:	
Glasgow Blatchford	0.69 (0.66 to 0.72)
AIMS65	0.78 (0.75 to 0.81)
Admission Rockall	0.76 (0.73 to 0.79)
Full Rockall	0.72 (0.68 to 0.77)
PNED	0.79 (0.76 to 0.82)

AUROC=Area under receiver operating characteristic curve.
Values represent all patients with available data.

- Current guidelines are based on a restrictive transfusion strategy – 70 g/L
- None of the current risk-scores predict specific blood transfusion requirements in patients with GIB
- Transfusion needs continue to change in patients with acute gastrointestinal bleeding

Villanueva, C. et al. *NEJM 2013*

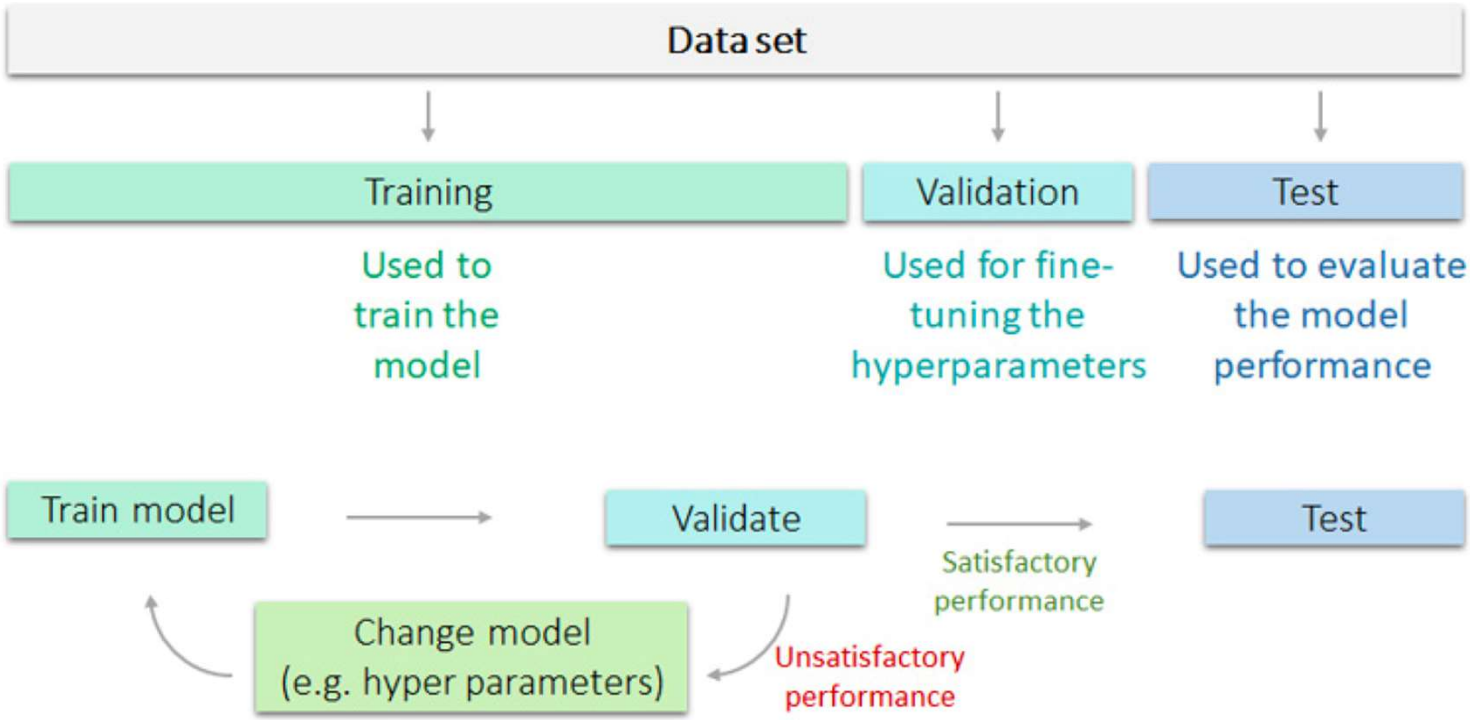


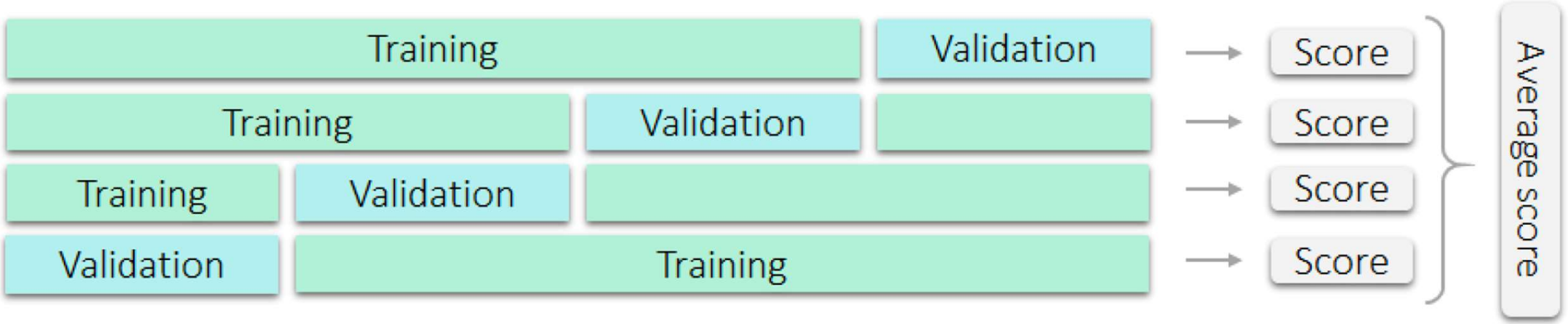
Risk prediction

Identification of radiology/ endoscopy images.

Propose optimal dosing based on feedback from previous experience

Shouval et al. *BJH.* 2020.





Van der Sommen et al. Gut. 2020.

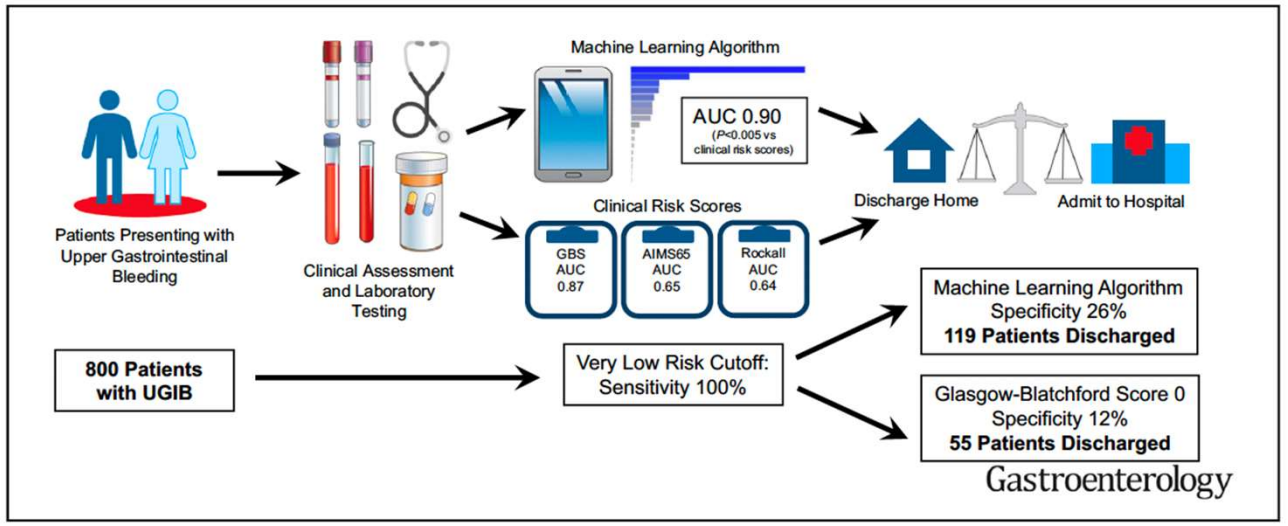
Gastroenterology 2020;158:160–167

CLINICAL AT

Validation of a Machine Learning Model That Outperforms Clinical Risk Scoring Systems for Upper Gastrointestinal Bleeding

Dennis L. Shung,[1] Benjamin Au,[1] Richard Andrew Taylor,[1] J. Kenneth Tay,[2] Stig B. Laursen,[3] Adrian J. Stanley,[4] Harry R. Dalton,[5] Jeffrey Ngu,[6] Michael Schultz,[7] and Loren Laine[1,8]

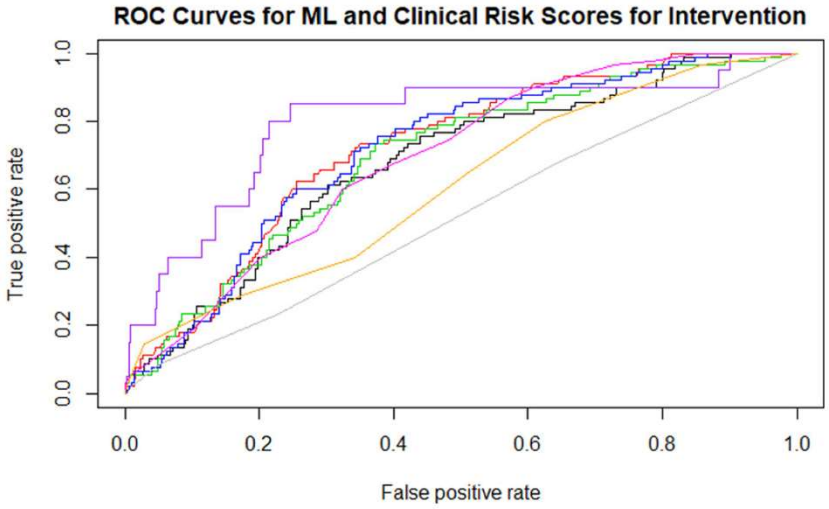
[1]Yale School of Medicine, New Haven, Connecticut; [2]Stanford University, Palo Alto, California; [3]Odense University Hospital, Odense, Denmark; [4]Glasgow Royal Infirmary, Glasgow, United Kingdom; [5]Royal Cornwall Hospital, Cornwall, United Kingdom; [6]Christchurch Hospital, Christchurch, New Zealand; [7]Dunedin Hospital, Dunedin, New Zealand; and [8]Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut

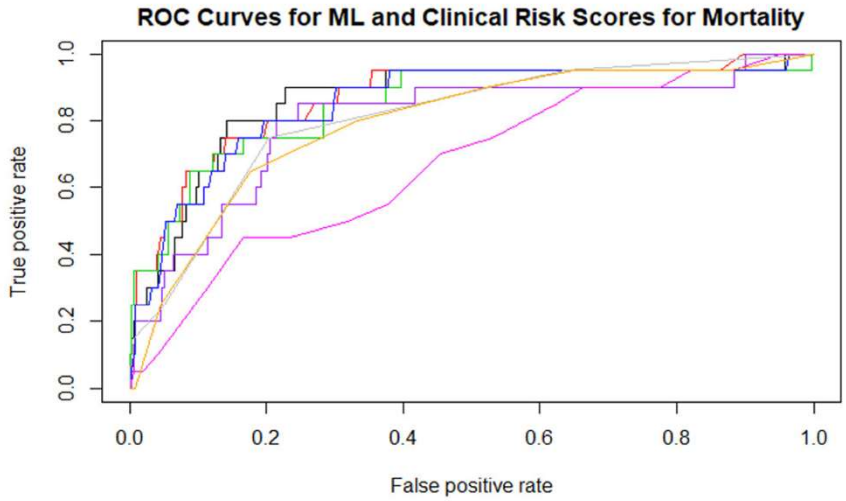


Performance of Machine Learning Model and Clinical Risk Assessment Scores

Composite endpoint[a]	Internal validation AUC (99% CI)	*P* value	External validation AUC (99% CI)	*P* value
XGBoost machine learning model	0.91 (0.90–0.93)		0.90 (0.87–0.93)	
Glasgow-Blatchford score	0.88 (0.86–0.90)	.001	0.87 (0.84–0.91)	.004
Admission Rockall score	0.69 (0.66–0.71)	<.001	0.65 (0.60–0.71)	<.001
AIMS65	0.72 (0.69–0.74)	<.001	0.64 (0.59–0.69)	<.001

[a]Red blood cell transfusion, hemostatic intervention (endoscopy, surgery, or interventional radiology), or 30-day mortality.





GBS : Pink
AIMS65 : Grey
Rockall: Orange

ML models: Black (neural network) , Red (random forest), Green (XGBoost), Purple (support vector machine), Blue (regression model)

scientific reports

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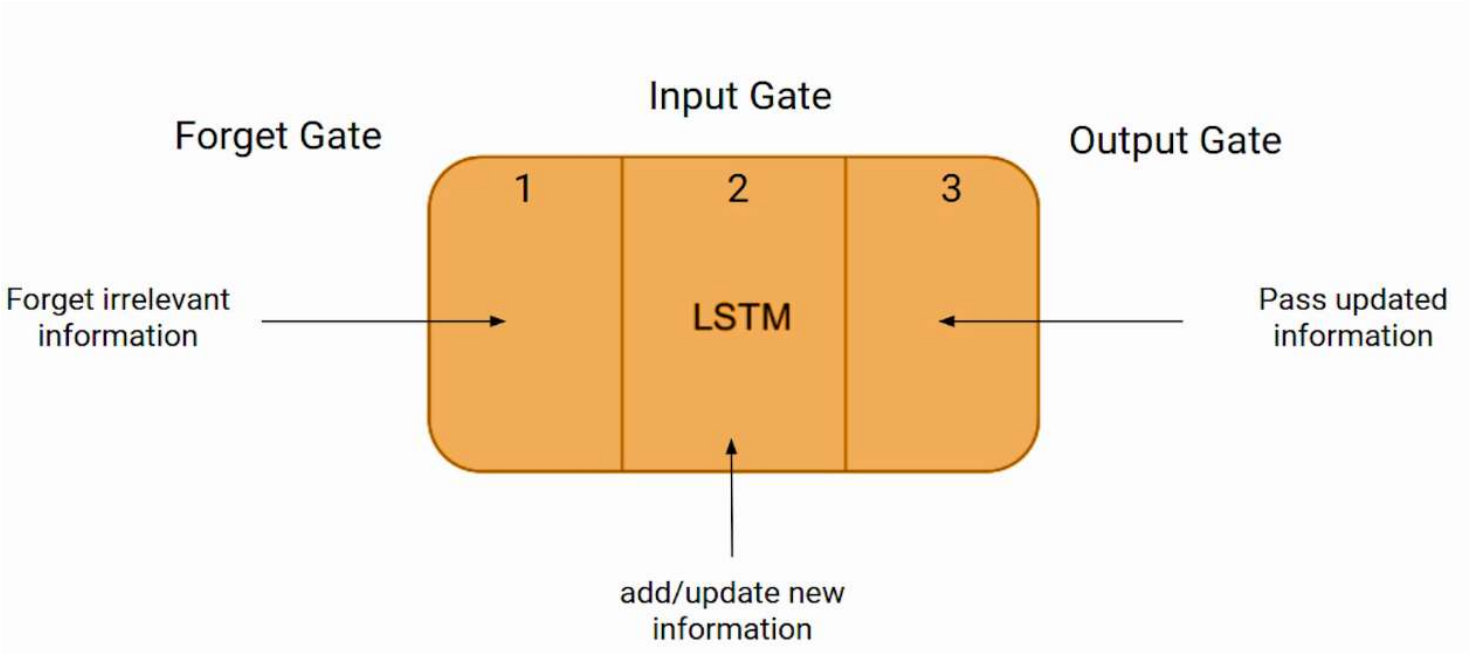
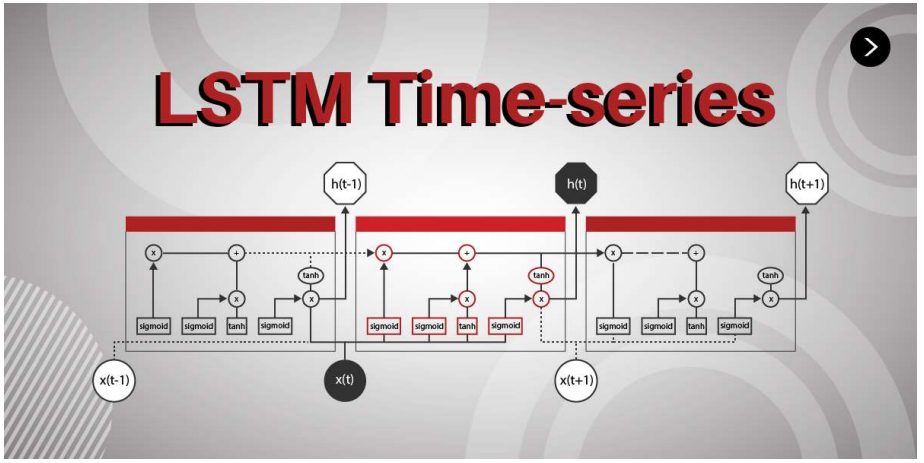
Neural network predicts need for red blood cell transfusion for patients with acute gastrointestinal bleeding admitted to the intensive care unit

Dennis Shung[1], Jessie Huang[3], Egbert Castro[2], J. Kenneth Tay[5], Michael Simonov[1], Loren Laine[1,4], Ramesh Batra[1] & Smita Krishnaswamy[3,6]✉


Input Gate
Forget Gate
Output Gate
1
2
3
Forget irrelevant information
LSTM
Pass updated information
add/update new information

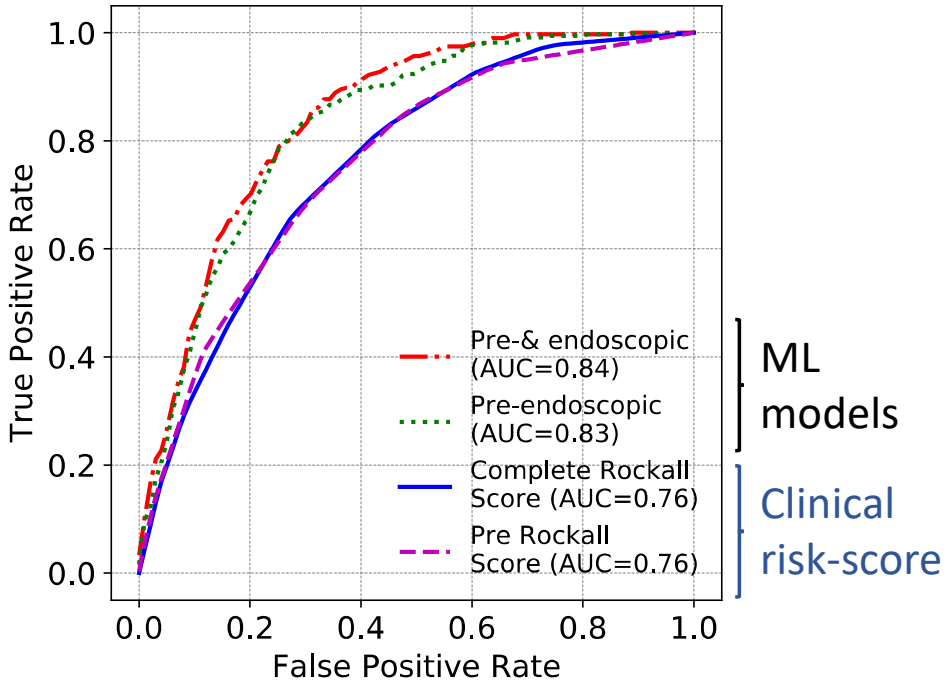

LSTM Time-series
h(t-1)
h(t)
h(t+1)
x(t-1)
x(t)
x(t+1)
sigmoid
tanh

	Long-short term memory network model AUROC 95% CI	Logistic Regression AUROC 95% CI	*p*-value	Regularized logistic regression with elastic net AUROC 95% CI	*p*-value
Internal Validation	0.81 (0.80–0.83)	0.75 (0.73–0.77)	< 0.001	0.75 (0.73–0.78)	< 0.001
External Validation	0.65 (0.61–0.69)	0.56 (0.51–0.60)	< 0.001	0.56 (0.52–0.61)	< 0.001

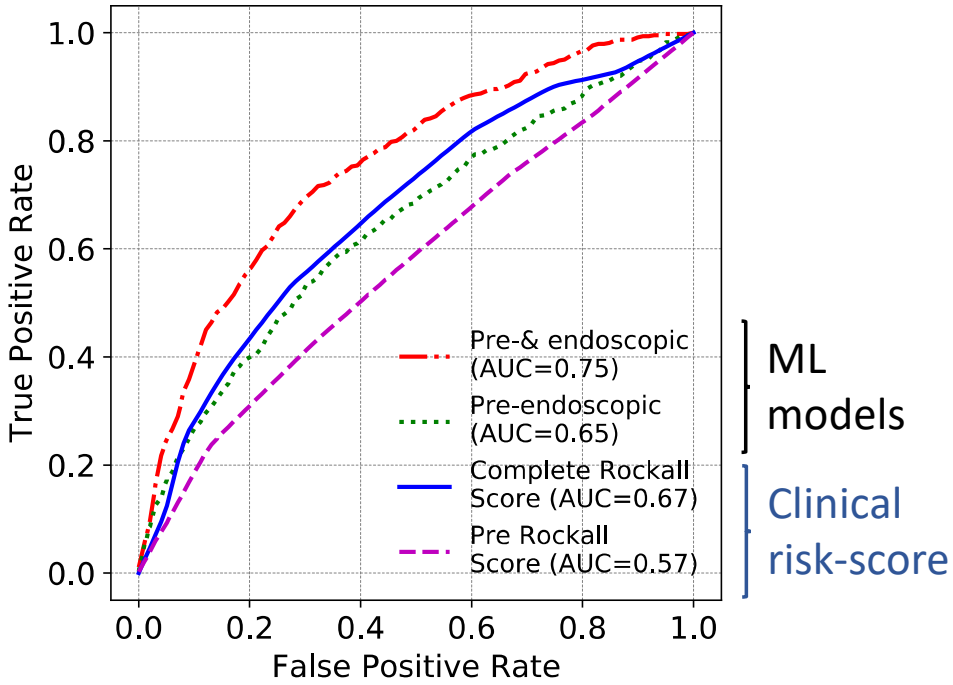
Table 3. Performance of the Long-Short Term Memory (LSTM) Model and the discrete time Logistic Regression (LR) model in Predicting Transfusion of Packed Red Blood Cells by Comparison of Area Under the Receiver Operating Curve (AUROC) for Internal Validation (N = 492) and External Validation (N = 1526).

Machine learning (ML) models

- Detect and model complex patterns using multiple variables from patient's medical information collected over different time points



ROC – 28-day all cause mortality



ROC – Rebleeding

Nigam G, et al. G*ut* 2021;**70:**A40.

Aim

- To develop and test a decision support tool (DST)
  - By applying ML on country-wide and electronic patient record (ePR) data of adult patients presenting with AUGIB
  - To support clinical management including transfusion practices and streamline resource allocation

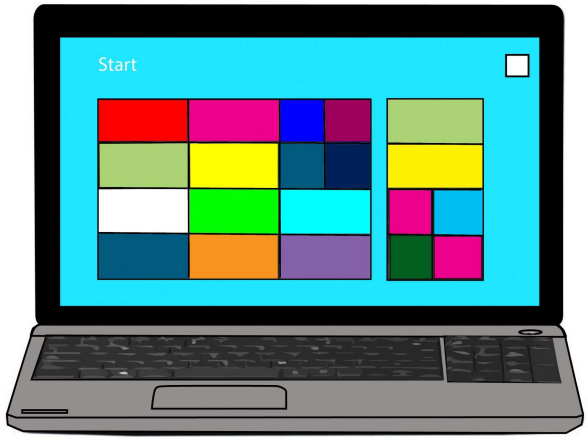
Primary Outcome

- Predicting composite need for hospital-based intervention or 30-day risk of dying

Secondary Outcomes

- Predicting early (5d) and late (30d) risk of dying; prediction of need for specific interventions, risk of rebleeding, length of stay

Decision Support Tool



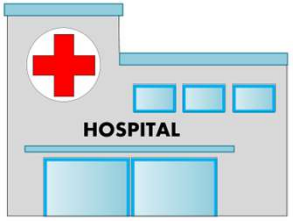
Demographics
Co-morbidities

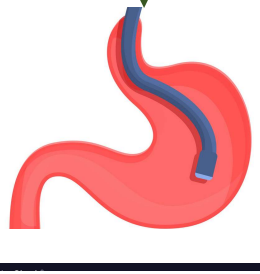
+ Clinical presentation +

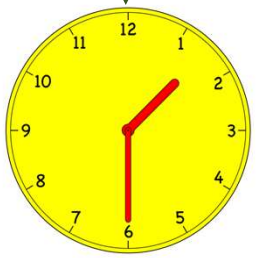
Clinical assessment
Laboratory testing

DST with validated ML models for outcomes

Explanation of feature selection for each outcome







- Length of stay

- Risk of dying

In summary

- Despite current guidelines recommending a restrictive approach to RBC transfusion in AUGIB, **a significant proportion of patients received early transfusions**

- **Early transfusion** was associated with an **elevated risk of re-bleeding and mortality, potentially due to liberal transfusion practices**, similar to the results noted in a 2007 prospective multi-centre observational study

- A one size fits all may not be applicable and whilst important to adhering to guidelines, adopting **individualized transfusion strategies for AUGIB patients** may be necessary

- Development of **clinical decision support tools** could help to optimize transfusion practice and improve clinical outcomes

Acknowledgements

Participating hospitals and site leads

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Questions??