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Absence of *Helicobacter pylori* is not protective against peptic ulcer bleeding in elderly on offending agents: lessons from an exceptionally low prevalence population

Aim *Helicobacter pylori* (*H. pylori*) infection is exceptionally rare in population from the north-eastern region of Peninsular Malaysia. This provides us an opportunity to contemplate the future without *H. pylori* in acute non-variceal upper gastrointestinal (GI) bleeding. *Methods* All prospective cases in the GI database registry with GI bleeding between 2003 and 2006 were reviewed. Cases with confirmed non-variceal aetiology were analysed. Rockall score > 5 was considered high risk for bleeding and primary outcomes studied were in-hospital mortality, recurrent bleeding and need for surgery. *Results* The incidence of non-variceal upper GI bleeding was 2.2/100,000 person-years. Peptic ulcer bleeding was the most common aetiology (1.8/100,000 person-years). In-hospital mortality (3.6%), recurrent bleeding (9.6%) and need for surgery (4.0%) were uncommon in this population with a largely low risk score (85.2% with score ≤ 5). Elderly were at greater risk for bleeding (mean 68.5 years, $P = 0.01$) especially in the presence of duodenal ulcers ($P = 0.04$) despite gastric ulcers being more common. NSAIDs (34%) and aspirin (22.8%) were the main risk factors. *Conclusions* The absence of *H. pylori* infection may not reduce the risk of peptic ulcer bleeding in the presence of risk factors especially offending drugs in the elderly.

1 **ORIGINAL ARTICLE**

2 **Absence of *Helicobacter pylori* is not protective against peptic ulcer**
3 **bleeding in elderly on offending agents: lessons from an**
4 **exceptionally low prevalence population**

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17 Running title: non-*H. pylori* ulcer bleeding in elderly

18 **ABSTRACT**

19 **Aim** *Helicobacter pylori* (*H. pylori*) infection is exceptionally rare in population from the north-
20 eastern region of Peninsular Malaysia. This provides us an opportunity to contemplate the future
21 without *H. pylori* in acute non-variceal upper gastrointestinal (GI) bleeding.

22 **Methods** All prospective cases in the GI database registry with GI bleeding between 2003 and
23 2006 were reviewed. Cases with confirmed non-variceal aetiology were analysed. Rockall score
24 > 5 was considered high risk for bleeding and primary outcomes studied were in-hospital
25 mortality, recurrent bleeding and need for surgery.

26 **Results** The incidence of non-variceal upper GI bleeding was 2.2/100,000 person-years. Peptic
27 ulcer bleeding was the most common aetiology (1.8/100,000 person-years). In-hospital mortality
28 (3.6%), recurrent bleeding (9.6%) and need for surgery (4.0%) were uncommon in this
29 population with a largely low risk score (85.2% with score ≤ 5). Elderly were at greater risk for
30 bleeding (mean 68.5 years, $P = 0.01$) especially in the presence of duodenal ulcers ($P = 0.04$)
31 despite gastric ulcers being more common. NSAIDs (34%) and aspirin (22.8%) were the main
32 risk factors.

33 **Conclusions** The absence of *H. pylori* infection may not reduce the risk of peptic ulcer bleeding
34 in the presence of risk factors especially offending drugs in the elderly.

35 **Keywords:** elderly, *Helicobacter pylori*, Malays, peptic ulcer, upper gastrointestinal bleeding

36 INTRODUCTION

37 Non-variceal upper gastrointestinal (GI) bleeding remains a prevalent condition and its
38 mortality hardly change despite declining trend of peptic ulcer disease and improvement in
39 therapeutic approaches. The reported incidence from North America and Europe was between 20
40 and 60/100,000 populations but data from Asia were unfortunately scarce and variable.¹ A recent
41 report from Thailand indicates an incidence of 152.9/100,000 population² and data from East
42 Malaysia (State of Sabah), available only in abstract, indicate an incidence of 72/100,000
43 population.³ Reports from two tertiary hospitals in central Peninsular Malaysia indicates an
44 overall low prevalence of non-variceal upper GI bleeding among the ethnic Malays,^{4, 5} possibly
45 due to a low prevalence of peptic ulcer disease in this population.⁶

46 There is a reducing trend of peptic ulcer disease observed within Asia, and this is largely a
47 result of reducing prevalence of *H. pylori* infection. This trend is likely to continue into the future
48 and a time will come when *H. pylori* joins the ranks of smallpox and polio.⁷ The population in the
49 north-eastern region of Peninsular Malaysia (state of Kelantan), that consists of 90% ethnic
50 Malays, has a seroprevalence of *Helicobacter pylori* (*H. pylori*) infection of only 4.2% among
51 496 blood donors and 4.8% among 921 patients attending a health screening clinic.⁸ The *H.*
52 *pylori* infection rate reported from gastric biopsies was 20% in duodenal ulcer, 21.2% in gastric
53 ulcer, 16.7% in duodenal erosion and 17.1% in gastric erosion.⁹ The incidence of peptic ulcer
54 perforations within the region from 1991 to 92 was only 1.5/100,000 person-years.⁸

55 The exceptional low prevalence of *H. pylori* in the population from north-eastern region of
56 Peninsular Malaysia provides us an opportunity to contemplate the future without the infection.
57 Our study aimed to determine the risk and clinical outcomes of acute non-variceal upper GI
58 bleeding in this population with low prevalence of *H. pylori* infection. The association between
59 clinical characteristics, risk factors and treatment given with risk and bleeding outcomes was also
60 assessed.

61 **METHODS**

62 **Study population**

63 We reviewed and analysed all prospective cases with a diagnosis of GI bleeding between 2003
64 and 2006 in our GI registry database. Cases were admitted in a tertiary university hospital
65 (Hospital XXX) situated in the north-eastern region of Peninsular Malaysia (State of Kelantan).
66 The region consists of 0.7 to 0.8 million of population (2003 – 2006) with a diverse racial
67 background but has a predominant Malay population of approximately 90%.

68 All adults above 18 years old with upper GI bleeding as a diagnosis in the GI registry were
69 then screened for inclusion. Subjects with typical symptoms and signs and subsequently requiring
70 upper endoscopy after informed consent and confirmed to have non-variceal causes of acute
71 upper GI bleeding were included into the analysis. Upper endoscopy was performed in all cases
72 within 24 hour upon admission. *H. pylori* status, where available, detected by either CLO test and
73 or histology during endoscopy, would also be recorded. Exclusion criteria included those patients
74 with lower GI bleeding, variceal bleeding, bleeding due to underlying hematologic disorders, GI
75 bleeding of unknown origin, and those patients who did not have an endoscopy examination.

76 The study was approved by the Human Ethics Committee of Universiti Sains Malaysia.

77 **Study outcome and definitions**

78 Rockall score⁹ was utilised to classify study population into low risk (score ≤ 5) and high risk
79 (score > 5)¹⁰ for non-variceal upper GI bleeding. Briefly, Rockall score is made up of five
80 variables, three of which are clinical parameters (age, shock and co-morbidities) and the other
81 two endoscopic features (causative lesions and stigmata of recent haemorrhage).^{9,11} Each variable
82 can be scored between 0 and 3, with a maximum score of 15 for all 5 variables.

83 The primary study outcome was to determine risk based upon the Rockall score, in-hospital
84 mortality, recurrent bleeding and the need for surgery in this population with non-variceal upper

85 GI bleeding. The secondary outcome was to determine the association between primary outcomes
86 with clinical characteristics, risk factors, endoscopic features and endoscopic treatment given.

87 In-hospital mortality was defined as death during the period of hospital stay which was
88 directly associated with upper GI bleeding and this was compared to patients still alive after 30
89 days. Recurrent bleeding was defined as new episode of bleeding during the period of hospital
90 stay after index bleeding had stopped, manifested as recurrence of symptoms and signs (fresh
91 blood in nasogastric aspirate) of bleeding and this was compared to those without bleeding after
92 index event. The need for surgery was defined as the need to undergo laparotomy after failure of
93 endoscopy interventions to stop bleeding and this was compared to those patients not needing any
94 surgical interventions after index bleed.

95 **Data and statistical analysis**

96 Data were presented in frequency and percentages unless otherwise stated. Statistical analysis
97 was performed with SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). Univariable and
98 multivariable analyses were used to test the association between variables. Receiver operating
99 characteristics (ROC) curve was utilised to determine the usefulness of Rockall score in
100 predicting the primary outcomes in this study population. A *P* value of < 0.05 was considered
101 statistically significant for all analyses.

102 **RESULTS**

103 **Incidence of upper GI bleeding and study population characteristics**

104 During the study period between 2003 and 2006, a total of 742 patients (incidence 6.5/100,000
105 person-years) were registered in the database with a diagnosis of GI bleeding. Of 742 patients,
106 250 patients (2.2/100,000 person-years) were subsequently identified and confirmed to have non-
107 variceal upper GI bleeding. The incidence of non-variceal bleeding was relatively similar
108 between gender with 1.3/100,000 person-years in men and 1/100,000 person-years in women.
109 Peptic ulcer bleeding was the primary aetiology of non-variceal bleeding in 204 patients
110 (1.8/100,000 person-years or 81.6% of total cases), of which 54% of cases were due to gastric
111 ulcer bleeding (Table 1). Only 2 cases were *H. pylori* positive and both cases were of non-Malays
112 in origin. The mean age of 250 patients was 62.1 years (range 15 – 97 years) with older patients,
113 at a mean age of 68.5 years, tended to have a higher risk score (*P* = 0.01).

114 **Primary outcome**

115 Majority of patients were of low risk on admission with 85.2% (213/250) of patients had a
116 Rockall score ≤ 5 and a mean Rockall score of 4.4. There were 3.6% (9/250) in-hospital
117 mortality, 9.6% (24/250) recurrent bleed and 4.0% (10/250) of patients who subsequently
118 required surgery. A higher Rockall score in this population was associated with increased in-
119 hospital mortality (mean score 7.0, $P < 0.001$), recurrent bleeding (mean score 5.1, $P = 0.01$) and
120 need for surgery (mean score 4.8, $P = 0.01$). A Rockall score > 5 was significant in predicting
121 recurrent bleeding in this population but only with area under curve or AUC of 0.6 (95% CI: 0.5-
122 0.7, $P = 0.04$) (Figure 1).

123 **Secondary outcome – clinical features, co-morbidities and other risk factors (Table 1 and 2)**

124 Peptic ulcer bleeding was more likely to re-bleed ($P = 0.04$) during hospitalisation (Table 1).
125 Duodenal ulcers (DU) were more likely to occur in the elderly (mean 66.2 years, $P = 0.04$) but no
126 difference in age was noted with gastric ulcers (GU) (mean 61.1 years with gastric ulcers vs. 63.2
127 years without gastric ulcers, $P = 0.3$). DUs, but not GUs or gastroduodenal ulcers/erosions, were
128 also associated with a higher risk score, mortality, recurrent bleeding and need for surgery (all P
129 < 0.05).

130 Symptoms of anaemia was associated with risk of recurrent bleeding ($P = 0.002$) and need for
131 surgery ($P = 0.02$) and epigastric pain was associated with increased need for surgery ($P = 0.005$)
132 (Table 1). A low hemoglobin level was associated with a higher risk score, in-hospital mortality,
133 recurrent bleeding and need for surgery (all $P < 0.05$). Recurrent bleeding was more common in
134 those patients with a raised urea ($P = 0.03$) and creatinine ($P = 0.03$). A raised urea was also more
135 likely to be associated with in-hospital mortality ($P = 0.04$).

136 Both chronic liver disease and septicaemia was significantly associated with increased in-
137 hospital mortality and recurrent bleeding (all $P < 0.05$) (Table 2). History of previous peptic ulcer
138 disease was associated with a higher risk score on admission ($P = 0.02$). More than 1/3 of patients
139 reported NSAIDs use but on its own, it was not associated with any of the studied outcomes on
140 univariate analysis (Table 2). Aspirin use was associated with recurrent bleeding ($P = 0.02$) but
141 warfarin use was associated in-hospital mortality ($P = 0.02$) (Table 2).

142 **Secondary outcome – endoscopic features and treatment (Table 3)**

143 Major stigmata of recent hemorrhage (SRH) were present in 26% of all bleeding and its
144 presence was associated with a higher risk score, in-hospital mortality, recurrent bleeding and

145 need for surgery (all $P < 0.05$). More than half were Forrest III lesions (57.2%) and GUs rather
146 than DUs were frequently Forrest III (41.2% vs. 8.4%). However, only Forrest III DUs were
147 associated with recurrent bleeding ($P = 0.04$). DUs were also more likely than GUs to have
148 Forrest I lesions (6.8% vs. 3.6%). Likewise, DUs rather than GUs were associated with a higher
149 risk score, mortality, recurrent bleeding and need for surgery (all $P < 0.05$). GUs were more
150 common than DUs to have Forrest II lesions (9.6% vs. 4.4%) but both were associated with a
151 higher risk score (both $P = 0.01$).

152 All patients admitted with GI bleeding received PPI used but there was no difference in
153 outcomes between omeprazole and pantoprazole. Blood transfusion was needed in 76% of all
154 bleeding and its requirement was associated with risk of recurrent bleeding ($P = 0.001$).
155 Endoscopic interventions were employed in 38.4% of all bleeding, with a third of these being
156 performed in high risk patients. Of all patients with bleeding, adrenaline was the sole intervention
157 in 17.2%, adrenaline with coagulation in 13.2% and adrenaline with clip in 8%. Use of adrenaline
158 only was associated with a higher risk score, recurrent bleeding and need for surgery (all $P <$
159 0.001). Likewise, adrenaline with clip therapy was associated with a higher risk score, recurrent
160 bleeding and need for surgery (all $P < 0.005$). Adrenaline with coagulation therapy was
161 associated with recurrent bleeding ($P = 0.02$) and need for surgery ($P = 0.005$).

162 **Secondary outcome – multivariable analysis (Table 4)**

163 Of the variables associated with a high Rockall score, major SRH was the factor most
164 predictive of high risk in this population (OR 25.2, 95% CI 8.5-74.3). This variable was also
165 associated with increased in-hospital mortality (OR 11.0, 95% CI 1.9 – 62.1). Likewise,
166 septicaemia was associated with a high risk score (OR 15.4, 95% CI: 2.9 – 81.1) and in-hospital
167 mortality (OR 27.1, 95% CI: 4.5-162.8). Warfarin use was the other risk factor associated with in-
168 hospital mortality (OR 16.7, 95% CI 2.1 – 132.5). Use of adrenaline only during endoscopic
169 intervention was the factor most associated with increased risk of recurrent bleeding (OR 4.4,
170 95% CI: 1.5–12.7) and need for surgery (OR 9.8, 95% CI: 2.3-43.9). Another factor associated
171 with recurrent bleeding was a raised creatinine (OR 1.002, 95% CI: 1.0-1.004). Epigastric pain
172 was highly predictive for increased need of surgery in this population (OR 6.3, 95% CI 1.2-32.2).

173 **DISCUSSION**

174 In this population starting with an exceptionally low prevalence of *H. pylori* infection, the
175 incidence of 2.2/100,000 person-years of non-variceal upper GI bleeding was also low. Peptic
176 ulcer bleeding was the most common cause with an incidence of 1.8/100,000 person-years and
177 this was almost similar to previously reported peptic ulcer perforation of 1.5/100,000 person-
178 years.⁸ Elderly in this population were more susceptible to non-variceal bleeding, especially from
179 DUs and had a higher risk score and concomitant co-morbidities, in keeping with recent
180 observation in *H. pylori*-eradicated populations.¹²

181 Rockall score > 5 may be useful in predicting recurrent bleeding in our population but the
182 AUC suggests that it may be less accurate and we did not assess other thresholds, which was a
183 limitation. Our study shared similar baseline characteristics with Vreeburg et al.¹³ including
184 definition for mortality but our results suggest a better prediction of recurrent bleeding rather than
185 in-hospital death. A higher rate of recurrent bleeding observed in our population as compared to
186 in-hospital mortality might explain this discrepancy. The low hemoglobin and urea levels
187 indicated a minor bleeding risk in general, compatible with the overall low risk score observed in
188 this population. The generally low risk score in this population does not, however, allow one to
189 decide for the need of therapeutic endoscopy. Blatchford score may have been more useful in this
190 regard.¹⁴

191 Among the variables described in Rockall score, SRH stood out as the most predictive of high
192 risk and in-hospital mortality. The presence of SRH was of greater significance in *H. pylori*-
193 associated bleeding GUs than DUs.¹⁵ In our study population, more than half of upper GI
194 bleeding was a result of GUs with only 20% due to DUs. However, GUs were more likely Forrest
195 III lesions (57.2%) but had relatively benign outcomes. In contrast, DUs, while less common, and
196 were more likely Forrest I and II lesions, but there was significant associations between DUs with
197 all studied outcomes. Previous studies have also similarly observed that *H. pylori*-negative DUs
198 are more likely to bleed and are more common among the elderly population with risk factors.^{16,17}
199 These studies were limited by false negative results for *H. pylori*, but our study population does
200 not suffer from this limitation.¹⁶

201 Septicaemia, while not a variable in the Rockall score, was also highly predictive of high risk
202 and in-hospital mortality, similarly reported by Zimmerman and others.^{18,19} In the original Rockall
203 validation study, pneumonia, which was associated with septicaemia was included in the model
204 but not in the complete model.⁹ Our study suggests that septicaemia, if present, should be
205 considered as a major co-morbidity and be given a score of 2. An elevated creatinine was
206 predictive for risk of recurrent bleeding in the multivariable analysis similarly reported by

207 Zuckerman and others^{20,21} Ischemic heart disease, the most common co-morbidity with substantial
208 mortality for GI bleeding also frequently have renal impairment.²²

209 Non-variceal upper GI bleeding was associated with more adverse outcomes in the current
210 study with a mostly elderly population, and an almost absence of *H. pylori* infection, and in the
211 presence of offending agents including aspirin, NSAIDs and warfarin. In a study from Japan, the
212 usage of aspirin and NSAIDs was not associated with a serious outcome in GU bleeding²³ but the
213 role of *H. pylori* infection was not addressed. Recent studies found that patients with *H. pylori*-
214 negative peptic ulcers and who took aspirin were more likely to have a higher bleeding risk.²⁴⁻²⁶ A
215 recent population-based study implicates warfarin, aspirin and NSAIDs in combination as
216 important aetiologies for upper GI bleeding.²⁷ Further studies are needed to determine the
217 significance of this finding since this also implicates *H. pylori*-eradicated populations over the
218 long term.

219 Endoscopic intervention was carried out in only a third of patients with high risk score and
220 this again implies that Rockall score is not useful to select those requiring interventions.
221 Endoscopic therapy with adrenaline only was associated with four-fold risk for recurrent bleeding
222 and approximately ten-fold risk for surgical intervention in the multivariable analysis similarly
223 reported by Levin et al.²⁸ This indicates that adrenaline alone is unlikely to be sufficient when
224 endoscopic intervention is needed.^{29,30}

225 The need for surgery is not an outcome initially included during the validation study of
226 Rockall score, however surgical intervention is frequently sought in the setting of failed
227 endoscopic therapy. In the current study, the need for surgical intervention of 4.0% was relatively
228 similar to the rate of in-hospital mortality of 3.6%. Previous study indicates an overall mortality
229 of 34.1% in patients with upper GI bleeding requiring surgery.³¹ Epigastric pain, predictive of the
230 need of surgery, might be a sign of impending perforation, and should be sought especially in this
231 rural-majority population who often present late in their course of disease.

232 Some limitations should be mentioned. We might not have captured all patients with upper GI
233 bleeding especially the more rural population. However, our hospital is the largest referral
234 institution within the region and we have a reliable GI registry. On the other hand, the current
235 study allowed us to understand the behaviour of non-variceal upper GI bleeding in an
236 environment not influenced by *H. pylori*, a confounder that affect most if not all the populations
237 in Asia.

238 So what the future would be like for non-variceal upper GI bleeding in the absence of *H.*
239 *pylori*? We can conclude that in our population with an exceptional low prevalence of *H. pylori*

240 infection and also peptic ulcer disease, acute non-variceal upper GI bleeding was also of low
241 incidence, similar to its peptic ulcer perforation rates. An absence of *H. pylori* infection may not
242 however reduce the risk of peptic ulcer bleeding in the presence of risk factors especially
243 offending drugs in an elderly population.

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248 **REFERENCES**

1. Sung JJ, Chan FK, Chen M, Ching JY, Ho KY, Kachintorn U, Kim N, Lau JY, Menon J, Rani AA, Reddy N, Sollano J, Sugano K, Tsoi KK, Wu CY, Yeomans N, Vakil N, Goh KL; Asia-Pacific Working Group. Asia-Pacific Working Group consensus on non-variceal upper gastrointestinal bleeding. *Gut* 2011; 60: 1170-7.
2. Sangchan A, Sawadpanitch K, Mairiang P, Chunlertrith K, Sukeepaisarnjaroen W, Sutra S, Thavornpitak Y. Hospitalized incidence and outcomes of upper gastrointestinal bleeding in Thailand. *J Med Assoc Thai* 2012; 95 Suppl 7: S190-5.
3. Cheng JLS, Gunn A, Menon J, Arokiasamy J, Ong P, Loong SY, Oommen G, Damodaran A. Aetiology of acute upper gastrointestinal bleeding in East Malaysia. *Med J Malaysia* 2001; 56 (supp A): D31.
4. Lim TM, Lu PY, Meheshinder S, Selvindoss P, Balasingh D, Ramesh J, Qureshi A. An audit of upper gastrointestinal bleeding at Seremban Hospital. *Med J Malaysia* 2003; 58: 522-5.
5. Lakhwani MN, Ismail AR, Barras CD, Tan WJ. Upper gastrointestinal bleeding in Kuala Lumpur Hospital, Malaysia. *Med J Malaysia* 2000; 55: 498-505.
6. Lee YY, Mahendra Raj S, Graham DY. Helicobacter pylori infection – A boon or a bane: lessons from studies in a low prevalence population. *Helicobacter* 2013; 18: 338-46.
7. Graham DY, Yamaoka Y, Malaty HM. Contemplating the future without *Helicobacter pylori* and the dire consequences hypothesis. *Helicobacter* 2007; 12 Suppl 2: 64-8.

8. Uyub AM, Raj SM, Visvanathan R, Nazim M, Aiyar S, Anuar AK, Mansur M. *Helicobacter pylori* infection in north-eastern peninsular Malaysia. Evidence for an unusually low prevalence. *Scand J Gastroenterol* 1994; 29: 209–213.
9. Raj SM, Yap K, Haq JA, Singh S, Hamid A. Further evidence for an exceptionally low prevalence of *Helicobacter pylori* infection among peptic ulcer patients in north-eastern peninsular Malaysia. *Trans R Soc Trop Med Hyg* 2001; 95: 24-7.
9. Rockall TA, Logan RFA, Devlin HB, Northfield TC. Risk assessment after acute upper gastrointestinal haemorrhage. *Gut* 1996; 38: 316-21.
- 10 Bessa X, O’Callaghan E, Balleste B, Nieto M, Seoane A, Panades A, Vazquez DJ, . Andreu M, Bory F. Applicability of the Rockall score in patients undergoing endoscopic therapy for upper gastrointestinal bleeding. *Dig Liver Dis* 2006; 38: 12-7.
11. Forrest JA, Finlayson ND, Shearman DJ. Endoscopy in gastrointestinal bleeding. *Lancet* 1974; 2: 394-7.
- 12 Domon K, Hirano N, Otsuka T, Fujitsuka Y, takeuchi M, Kikuchi Y, Nakano S, . Igarashi Y. Clinical evaluation of hemorrhagic gastroduodenal ulcer in the elderly: is *Helicobacter pylori* infection a risk factor for haemorrhage? *Dig Endosc* 2012; 25: 319-24.
- 13 Vreeburg EM, Terwee CB, Snel P, Rauws EA, Bartelsman JF, Meulen JH, Tytgat . GN. Validation of the Rockall risk scoring system in upper gastrointestinal bleeding. *Gut* 1999; 44: 331-5.
- 14 Pang SH, Ching JY, Lau JY, Sung JJ, Graham DY, Chan FK. Comparing the . Blatchford and pre-endoscopic Rockall score in predicting the need for endoscopic therapy in patients with upper GI haemorrhage. *Gastrointest Endosc* 2010; 71: 1134-40.
- 15 Chang-Chien CS, Wu CS, Chen PC, Lin DY, Chu CM, Fang KM, Sheen IS, Liaw . YF. Different implications of stigmata of recent haemorrhage in gastric and duodenal ulcers. *Dig Dis Sci* 1988; 33: 400-4.
- 16 Gisbert JP, Calvet X. Review article: *Helicobacter pylori*-negative duodenal ulcer . disease. *Aliment Pharmacol Ther* 2009; 30: 791-815.
- 17 Chu KM, Kwok KF, Law S, Wong KH. Patients with *Helicobacter pylori* positive

- and negative duodenal ulcers have distinct clinical characteristics. *World J Gastroenterol* 2005; 11: 3518-22.
- 18 Zimmerman J, Meroz Y, Arnon R, Tsvang E, Siguencia J. Predictors of mortality in hospitalized patients with secondary upper gastrointestinal haemorrhage. *J Intern Med* 1995; 237: 331-7.
- 19 Afessa B. Systemic inflammatory response syndrome in patients hospitalized for gastrointestinal bleeding. *Crit Care Med* 1999; 27: 554-7.
- 20 Zuckermann GR, Cornette GL, Clouse RE, Harter HR. Upper gastrointestinal bleeding in patients with chronic renal failure. *Ann Intern Med* 1985; 102: 588-92.
- 21 Sood P, Kumar G, Nanchal R, Sakhuja A, Ahmad S, Ali M, Kumar N, Ross EA. Chronic kidney disease and end-stage renal disease predict higher risk of mortality in patients with primary upper gastrointestinal bleeding. *Am J Nephrol* 2012; 35: 216-24.
- 22 Shalev A, Zahger D, Novack V, Etzion O, Shimony A, Gilutz H, Cafri C, Ilia R, Fich A. Incidence, predictors and outcome of upper gastrointestinal bleeding in patients with acute coronary syndromes. *Int J Cardiol* 2012; 157: 386-90.
- 23 Ishikawa S, Inaba T, Mizuno M, Okada H, Kuwaki K, Kuzuma T, Yokota H, Fukuda Y, Takeda K, Nagano H, Wato M, Kawai K. Incidence of serious gastrointestinal bleeding in patients taking non-steroidal anti-inflammatory drugs in Japan. *Acta Med Okayama* 2008; 62: 29-36.
- 24 Kang JM, Kim N, Lee BH, Park HK, Jo HJ, Shin CM, Lee SH, Park YS, Hwang JH, Kim JW, Jeong SH, Lee DH, Jung HC, Song IS. Risk factors for peptic ulcer bleeding in terms of *Helicobacter pylori*, NSAIDs and antiplatelet agents. *Scand J Gastroenterol* 2011; 46: 1295-301.
- 25 Chan FK, Ching JY, Suen BY, Tse YK, Wu JC, Sung JJ. Effects of *Helicobacter pylori* infection on long-term risk of peptic ulcer bleeding in low-dose aspirin users. *Gastroenterology* 2013; 144: 528-35.
- 26 Hernandez-Diaz S, Garcia Rodriguez LA. Cardioprotective aspirin users and their excess risk of upper gastrointestinal complications. *BMC Med* 2006; 4: 22.
- 27 Hreinsson JP, Kalaitzakis E, Gudmundsson S, Bjornsson ES. Upper gastrointestinal bleeding: incidence, etiology and outcomes in a population-based

setting. *Scand J Gastroenterol* 2013; 48: 439-47.

- 28 Levin DA, Watermeyer GA, Deetleefs E, Metz DC, Thomson SR. The efficacy of endoscopic therapy in bleeding peptic ulcer patients. *S Afr Med J* 2012; 102: 290-3.
- 29 Chung SS, Lau JY, Sung JJ, Chan AC, Lai CW, Ng EK, Chan FK, Yung MY, Li AK. Randomised comparison between adrenaline injection alone and adrenaline injection plus heat probe treatment for actively bleeding ulcers. *BMJ* 1997; 314: 1307-11.
- 30 Chung IK, Ham JS, Kim HS, Park SH, Lee MH, Kim SJ. Comparison of the hemostatic efficacy of the endoscopic hemoclip method with hypertonic saline-epinephrine injection and a combination of the two for the management of bleeding peptic ulcers. *Gastrointest Endosc* 1999; 49: 13-8.
- 31 Czymek R, Großmann A, Roblick U, Schmidt A, Fischer F, Bruch HP, Hildebrand P. Surgical management of acute upper gastrointestinal bleeding: still a major challenge. *Hepatogastroenterology* 2012; 59: 768-73.

249 LEGEND:

250 **Figure 1:** The usefulness of Rockall score in predicting outcomes in non-variceal upper
251 gastrointestinal bleeding in this ethnic Malay-majority population

Table 1 (on next page)

Clinical characteristics of study population

n; frequency, SEM; standard error of mean, # significant P value < 0.05 (Fisher's exact or Pearson Chi-Square test for categorical and t-test for continuous variables)

Table 1: Clinical characteristics of study population

Parameters	All	High risk	Mortality	Recurrent bleeding	Need for surgery
Age, years, mean (SEM)	62.1 (1.0)	68.5 (2.6) [#]	60.5 (7.4)	60.5 (3.4)	62.4 (4.5)
Gender, n (%)					
Male	144 (57.6)	20 (8.0)	5 (2.0)	17 (6.8)	8 (3.2)
Female	106 (42.4)	17 (6.8)	4 (1.6)	7 (2.8)	3 (1.2)
Ethnic, n (%)					
Malays	209 (83.6)	31 (12.4)	7 (2.8)	22 (8.8)	11 (100)
Non-Malays	41 (16.4)	6 (2.4)	2 (0.8)	2 (0.8)	0
Causative lesions, n (%)					
Peptic Ulcer	204 (81.6)	32 (12.8)	9 (3.6)	24 (9.6) [#]	10 (4.0)
Gastric ulcer	135 (54.0)	15 (6.0)	3 (1.2)	10 (4.0)	4 (1.6)
Duodenal ulcer	49 (19.6)	17 (6.8) [#]	6 (2.4) [#]	14 (5.6) [#]	6 (2.4) [#]
Gastroduodenal ulcers/erosions	20 (8.0)	0	0	0	0
Gastroduodenitis	36 (14.4)	4 (1.6)	0	0	0
Others (tumours, telangiectasia)	10 (4.0)	1 (0.4)	0	0	0
Presenting symptoms, n (%)					
Melaena	189 (75.6)	32 (12.8)	6 (2.4)	22 (8.8)	11 (4.4)
Haematemesis	117 (46.8)	16 (6.4)	4 (1.6)	9 (3.6)	3 (1.2)
Epigastric pain	103 (41.2)	16 (6.4)	2 (0.8)	11 (4.4)	9 (3.6) [#]
Anaemia	168 (67.2)	30 (12.0) [#]	8 (3.2)	23 (9.2) [#]	11 (4.4) [#]
Laboratory parameters, mean (SEM)					
Hemoglobin (g/dl)	8.2 (0.2)	7.3 (0.4) [#]	6.5 (0.7) [#]	6.7 (0.3) [#]	6.3 (0.4) [#]
Platelet (x 10 ³ /mm ³)	292.3 (10.4)	261.9 (25.3)	248.9 (43.1)	339.7 (50.4)	375 (51.4)
INR	1.3 (0.05)	1.4 (0.1)	2.0 (0.4)	1.4 (0.1)	1.3 (0.1)
aPTT (seconds)	33.9 (0.8)	37.9 (1.6) [#]	39.9 (4.2)	38.8 (3.3)	35.4 (2.2)
Urea (mmol/l)	14.1 (0.8)	18.3 (2.4)	22.5 (4.5) [#]	21.0 (3.2) [#]	20.3 (4.4)
Creatinine (mmol/l)	170.9 (13.6)	196.3 (35.1)	316.9 (96.4)	290.4 (54.4) [#]	217.8 (54.1)

Legend: n; frequency, SEM; standard error of mean, # significant *P* value < 0.05 (Fisher's exact or Pearson Chi-Square test for categorical and t-test for continuous variables)

Table 2(on next page)

Co-morbidities and risk factors

n; frequency, # significant P value <0.05 (Fisher's exact test or Pearson Chi-Square test for categorical and t-test for continuous variables)

Table 2: Co-morbidities and risk factors

Parameters	All	High risk	Mortality	Recurrent bleeding	Need for surgery
Co-morbidities, n (%)					
Ischemic heart disease	53 (21.2)	14 (5.6) [#]	2 (0.8)	1 (0.4)	0
Chronic renal failure	41 (16.4)	12 (4.8) [#]	2 (0.8)	7 (2.8)	3 (1.2)
Chronic liver disease	11 (4.4)	4 (1.6) [#]	2 (0.8) [#]	3 (1.2) [#]	1 (0.4)
Diabetes Mellitus	59 (23.6)	11 (4.4)	4 (1.6)	8 (3.2)	3 (1.2)
Malignancies	17 (6.8)	1 (0.4)	4 (1.6)	4 (1.6)	1 (0.4)
Septicaemia	12 (4.8)	6 (2.4) [#]	4 (1.6) [#]	4 (1.6) [#]	1 (0.4)
Risk factors, n (%)					
Previous peptic ulcer disease	41 (16.4)	11 (4.4) [#]	1 (0.4)	6 (2.4)	2 (0.8)
NSAIDs	85 (34.0)	12 (4.8)	3 (1.2)	11 (4.4)	5 (2.0)
Aspirin	57 (22.8)	9 (3.6)	2 (0.8)	1 (0.4) [#]	0
Clopidogrel	23 (9.2)	6 (2.4)	1 (0.4)	0	0
Warfarin	13 (5.2)	4 (1.6)	2 (0.8) [#]	0	0
Corticosteroids	10 (4.0)	1 (0.4)	0	2 (0.8)	1 (0.4)
Herbs/traditional medicine	4 (1.6)	2 (0.8)	0	0	0

Legend: n; frequency, # significant *P* value <0.05 (Fisher's exact test or Pearson Chi-Square test for categorical and t-test for continuous variables)

Table 3(on next page)

Endoscopic features and treatment given

n; frequency, # significant P value <0.05 (Fisher's exact test or Pearson Chi-Square test for categorical and t-test for continuous variables)

Table 3: Endoscopic features and treatment given

Parameters	All	High risk	Mortality	Recurrent bleeding	Need for surgery
Stigmata of recent haemorrhage, n (%)					
None or dark spots	185 (74.0)	9 (3.6)	2 (0.8)	10 (4.0)	3 (1.2)
Major stigmata	65 (26.0)	28 (11.2) [#]	7 (2.8) [#]	14 (6.4) [#]	7 (2.8) [#]
Forrest classification, n (%)					
Forrest I (a: spurting, b: oozing)	26 (10.4)	13 (5.2) [#]	5 (2.0) [#]	11 (4.4) [#]	6 (2.4) [#]
Gastric ulcer	9 (3.6)	3 (1.2)	1 (0.4)	3 (1.2)	3 (1.2)
Duodenal ulcer	17 (6.8)	10 (4.0) [#]	4 (1.6) [#]	8 (3.2) [#]	3 (1.2) [#]
Forrest II (a: vessel, b: clot, c: haematin)	35 (14.0)	13 (5.2) [#]	1 (0.4)	3 (1.2)	2 (0.8)
Gastric ulcer	24 (9.6)	8 (3.2) [#]	0	2 (0.8)	1 (0.4)
Duodenal ulcer	11 (4.4)	5 (2.0) [#]	1 (0.4)	1 (0.4)	1 (0.4)
Gastroduodenal ulcers	1 (0.4)	0	0	0	0
Forrest III (clean base)	143 (57.2)	2 (0.8)	1 (0.4)	5 (2.0)	2 (0.8)
Gastric ulcer	103 (41.2)	4 (1.6) [#]	2 (0.8)	5 (2.0)	0
Duodenal ulcer	21 (8.4)	2 (0.8)	1 (0.4)	5 (2.0) [#]	2 (0.8)
Gastroduodenal ulcers	19 (7.6)	0	0	0	0
Type of PPI, n (%)					
Omeprazole	42 (16.8)	6 (2.4)	0	2 (0.8)	0
Pantoprazole	208 (83.2)	31 (12.4)	9 (3.6)	22 (8.8)	10 (4.0)
Tranfusion requirement, n (%)					
Yes	190 (76.0)	32 (12.8)	9 (3.6)	24 (9.6) [#]	10 (4.0)
No	60 (24.0)	5 (2.0)	0	0	0
Endoscopic intervention, n (%)					
Adrenaline only	43 (17.2)	14 (5.6) [#]	4 (1.6)	12 (4.8) [#]	7 (2.8) [#]
+ coagulation	33 (13.2)	7 (2.8)	2 (0.8)	7 (2.8) [#]	5 (2.0) [#]
+ clip	20 (8.0)	10 (4.0) [#]	0	8 (3.2) [#]	4 (1.6) [#]

Legend: n; frequency, # significant *P* value <0.05 (Fisher's exact test or Pearson Chi-Square test for categorical and t-test for continuous variables)

Table 4(on next page)

Results of multiple logistic regression analysis (forward: LR)

LR; likelihood ratio, OR; adjusted odd ratio, CI; confidence interval

Table 4: Results of multiple logistic regression analysis (forward: LR)

Outcome and risk factors	OR	95% CI for OR	P value
High risk			
Major stigmata of bleeding	25.2	8.5 – 74.3	< 0.001
Septicaemia	15.4	2.9 – 81.1	0.001
Chronic renal failure	4.1	1.3 – 12.6	0.01
Ischemic heart disease	3.4	1.2 – 9.7	0.02
Age	1.05	1.0 – 1.1	0.004
In-hospital mortality			
Septicaemia	27.1	4.5 – 162.8	< 0.001
Warfarin	16.7	2.1 – 132.5	0.008
Major stigmata of bleeding	11.0	1.9 – 62.1	0.007
Recurrent bleeding			
Adrenaline only	4.4	1.5 – 12.7	0.006
Creatinine	1.002	1.0 – 1.004	0.04
Need for surgery			
Adrenaline only	9.8	2.3 – 41.9	0.002
Epigastric pain	6.3	1.2 – 32.2	0.03

Legend: LR; likelihood ratio, OR; adjusted odd ratio, CI; confidence interval

Figure 1

Figure 1

The usefulness of Rockall score in predicting outcomes in non-variceal upper gastrointestinal bleeding in this ethnic Malay-majority population

