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***Retrospective Cohort Study***

**Mortality associated with gastrointestinal bleeding in children: A retrospective cohort study**

Attard TM *et al*. Mortality associated with pediatric gastrointestinal hemorrhage

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**Abstract**

***AIM***

To determine the clinical characteristics of children with gastrointestinal bleeding (GIB) who died during the course of their admission.

***METHOD***

We interrogated the Pediatric Hospital Information System database, including International Classification of Diseases, Current Procedural Terminology and Clinical Transaction Classification coding from 47 pediatric tertiary centers extracting the population of patients (1-21 years of age) admitted (inpatient or observation) with acute, upper or indeterminate GIB (1/2007-9/2015). Descriptive statistics, unadjusted univariate and adjusted multivariate analysis of the associations between patient characteristics and treatment course with mortality was performed with mortality as primary and endoscopy a secondary outcome of interest. All analyses were performed using the R statistical package, v.3.2.3.

***RESULTS***

The population with GIB was 19,528; 54.6% were male, overall mortality was 2.07%; (0.37% in patients with the principal diagnosis of GIB). When considering only the mortalities in which GIB was the principal diagnosis, 48% (12 of 25 principal diagnosis GIB mortalities) died within the first 3 d of admission, whereas 19.8% of secondary diagnosis GIB patients died with 3 d of admission. Patients who died were more likely to have received octreotide (19.8% *c.f.* 4.04%) but tended to have not received PPI therapy in the first 48 h, and far less likely to have undergone endoscopy during their admission (OR = 0.489, *P* < 0.0001). Chronic liver disease associated with a greater likelihood of endoscopy. Mortalities were significantly more likely to have multiple complex chronic conditions.

***CONCLUSION***

GIB associated mortality in children is highest within 7 d of admission. Multiple comorbidities are a risk factor whereas early endoscopy during the admission is protective.

**Key words:** Pediatrics; Gastrointestinal hemorrhage; Endoscopy; Proton pump inhibitors; Octreotide; Mortality; Liver disease; Hospital Information Systems

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**Core tip:** The management of gastrointestinal haemorrhage in children is challenging insofar as the timing and impact of different interventions remains poorly defined. The authors analysed the characteristics and associated interventions associated with mortality as an outcome with gastrointestinial bleeding in children past infancy. Death associated with gastrointestinal haemorrhage was reported in 2% overall albeit less (0.4%) in the cohort with haemorrhage as admitting diagnosis. Patients who died were far less likely to have undergone endoscopy during the admission and more likely to have received octreotide and less likely to have received proton pump inhibitor therapy during the first two days of admission.

Attard TM, Miller M, Pant C, Kumar A, Thomson M. mortality associated with gastrointestinal bleeding in children: a retrospective cohort study. *World J Gastroenterol* 2016; In press

**INTRODUCTION**

 Gastrointestinal bleeding (GIB) is a foremost indication for emergent diagnostic and therapeutic endoscopy requiring prompt, including disease-specific pharmacotherapy[1,2]. Although acute GIB in adults has been exhaustively studied including epidemiology and predictors of adverse outcomes, there is a paucity of the corresponding evidence in children[3,4]. This deficit hinders the evidence based allocation of resources and the implementation of standardized protocols, potentially adversely impacting outcomes in children.

One of the co-authors, has identified the presence of > 3 comorbid conditions, presentation to a teaching hospital, the presence of upper GI bleeding; age under 5 years and health coverage with private insurance as independent risk factors associated with an increased rate of hospital admission with GI bleeding[5]. Hemorrhage occurred in 0.5% of all discharges from inpatient care, was more prevalent in males and older than 11 years. Esophageal and intestinal perforation were identified as at highest risk of associated mortality, together accounting for 17% of all patients with GI haemorrhage and who died[6].

Disease classification in adult GIB cannot be extrapolated to the pediatric population. Risk factors identifiable in adults, foremost amongst which are age, NSAID, SSRI, aspirin, antiplatelet and anticoagulant therapy and chronic renal and cardiovascular disease, are clearly not applicable to children[7]. Conversely, the impact of predominantly pediatric and especially neonatal disease processes (*e.g.* prematurity) on the risk of GIB remain unknown. This limits the applicability of pre- and postendoscopic predictive scoring systems [Rockall, Blatchford (aka Glasgow), Addenbrooke] to identify patients at high risk (need for blood transfusion, surgical intervention, rebleeding and mortality) and those requiring immediate endoscopic intervention as opposed to at low risk who can be safely discharged[8-10]. The Sheffield Scoring system is, to date the only successful attempt at predicting the need for endoscopic hemostatic intervention based on the clinical presentation, hemodynamic parameters and need for blood products[11]. An understanding of the epidemiologic context of GIB in children holds the promise of directing future research toward improving predictive models of disease outcomes including mortality.

The Pediatric Health Information System (PHIS) database is a repository of diagnostic, therapeutic and procedure records from 48 regional pediatric tertiary centers in the United States that has been in existence since 2004, the data is available in de-identified form to health information management administrators and academicians in the respective institutions.

Herein we report on the PHIS recorded demographic and clinical profile of children with upper or indeterminate gastrointestinal bleeding at admission or during their inpatient course and resulting in death.

**Materials and methods**

### ***Data source***

We conducted a retrospective cohort study using data obtained from the PHIS, an administrative database that contains inpatient, emergency department, ambulatory surgery and observation encounter-level data from 49 not-for-profit, tertiary care pediatric hospitals in the United States. The PHIS hospitals are 49 of the largest and most advanced children's hospitals in America, and constitute the most demanding standards of pediatric service in America. These hospitals are affiliated with the Children’s Hospital Association (Overland Park, KS, United States). Data quality and reliability are assured through a joint effort between the Children’s Hospital Association and participating hospitals. Portions of the data submission and data quality processes for the PHIS database are managed by Truven Health Analytics (Ann Arbor, MI, United States). For the purposes of external benchmarking, participating hospitals provide discharge/encounter data including demographics, diagnoses, and procedures. Nearly all of these hospitals also submit resource utilization data (*e.g.* pharmaceuticals, imaging, and laboratory) into PHIS. Data are de-identified at the time of data submission, and data are subjected to a number of reliability and validity checks before being included in the database. For this study, data from 47 hospitals was included. This study was approved by the Institutional Review Board (16050358).

***Study patients***

Children between the ages of 1 and 21 years at the time of admission were eligible for inclusion if they were diagnosed with an upper gastrointestinal bleed (UGIB) or GIB of indeterminate location and admitted as an inpatient or under observation with Emergency Department charges between January 1, 2007 and September 30, 2015. Study participants with UGIB were identified through International Classification of Diseases, Ninth Revision (ICD-9) discharge diagnosis codes (Supplementary Table 1).

Demographic characteristics included age in years at time of admission, sex, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian, Other, Unknown), discharge disposition (routine/home, expired and rural vs. urban zip code of residence. Complex chronic conditions (CCCs) were defined using a previously described ICD-9 coding scheme for 9 types of CCCs (neuromuscular, cardiovascular, respiratory, renal, gastrointestinal, hematologic/immunologic, metabolic, congenital or genetic, and malignancy), as well as organ transplant patients and technology dependent patients[12]. A given patient could have could have more than 1 CCC, and the total number of CCCs for each patient was calculated. Chronic liver disease was also identified by ICD-9 diagnosis codes, and coded as a dichotomous variable. The need for packed red blood cell transfusions was used to control for severity of bleeding (0 = no transfusion, 1 = transfusion(s) received).

Procedures were identified through ICD-9-CM codes (Supplementary Table 2), and pharmaceuticals and imaging procedures were identified through Clinical Transaction Classification system for revenue codes.

***Outcome measures***

The primary outcome of interest in this study was mortality. Secondary outcomes examined include whether or not the patient underwent endoscopy.

***Statistical analysis***

Unadjusted, univariate analyses of the associations between patient characteristics and treatment course with mortality were carried out. Continuous variables were summarized using the median and interquartile ranges (IQR) and compared using the Wilcoxon rank-sum test. Categorical variables were summarized using counts and frequency as a percentage, and compared using the *χ2*test of association or Fisher's exact test, where appropriate. Complex chronic conditions were treated categorically as the number of complex chronic conditions present in a single patient. The levels of the category were defined as 0 complex chronic conditions, 1 or 2 complex chronic conditions, and 3 or more complex chronic conditions. These levels were chosen after assessing the median and inter-quartile range of the distribution of number of CCCs. Receipt of pharmaceuticals on the first or second day of admission was coded as a dichotomous variable, as was the receipt of packed red blood cell transfusions and platelet transfusions. All procedures were coded as 0 (procedure not billed) or 1 (procedure billed). Unadjusted *P*-values were reported for the univariate analysis.

Adjusted analysis of the association between patient characteristics and treatment course with mortality were examined using multivariable generalized linear mixed models to assess the odds of exposure to treatment among mortality cases (binomial family, logit link). A quasi-likelihood method was used to estimate effects (Laplace approximation). All candidate models were adjusted for potential confounding by age in years at admission, race/ethnicity, and sex and by the need for packed red blood cell transfusions as a surrogate of severity of bleed. Chronic liver disease, comorbid complex chronic conditions, and urban *vs* rural zip code of residence at time of admission were tested as covariates. Other covariates included perforation type injury, administration of PPI, H2RA, octreotide, and vasopressin pharmaceuticals on the first or second day of admission and endoscopic procedures performed. Interactions between vasopressin and shock, endoscopy and chronic liver disease, and endoscopy and CCCs were also tested to investigate potential effect modification. To account for increased variability due to clustering within hospitals, a random intercept was included using a unique hospital ID. Model selection was carried out using -2 log likelihood tests with the *χ2*approximation. Individual covariates were tested by approximation to the *Z*-value. The Holm procedure was used to account for multiple testing of covariates for each outcome, and the adjusted *P*-values are reported for the significance test of model covariates. An adjusted, two-tailed *P* < 0.05 was considered statistically significant. All analyses were performed using the R statistical package, v. 3.2.3.

**RESULTS**

***Descriptive statistics***

There were 19,528 patients with upper or indeterminate GIB discharged between January 1, 2007 and September 30, 2015 (Table 1). Overall, 54.6% of patients were male, and the median age was 9 years [IQR (4, 15)]. Nearly half (49.68%) of the patients had no documented CCCs, 30.32% had 1 or 2 CCCs, and 20.01% had 3 or more CCCs. The most common CCC was gastrointestinal conditions (28.22%), followed by technology dependence[12,13] (20.24%) and neurologic and neuromuscular disorders (13.90%) (Table 5). Of the patients included in the analysis, 33.78% experienced hematemesis, 40.97% melena, 12.18% had gastroesophageal reflux (GER), 3.73% experienced shock, 3.56% experienced sepsis, and 18.45% required packed red blood cell transfusion while 5.09% required a platelet transfusion. Most patients resided in an urban area (85.31%), although a small portion of the data was missing (2.16%).

Overall mortality rate was 2.07% with 0.37% mortality among patients with principal diagnosis of GIB and 2. 96% among patients with secondary diagnosis of GIB. The median time until death was 19 d (5, 49). For all patients, 21.53% of deaths occurred within the first 3 days of admission, and 31.9% occurred within 7 d of admission. When considering only the mortalities in which GIB was the principal diagnosis, 48% (12 of 25 principal diagnosis GIB mortalities) died within the first 3 d of admission, and 64% expired within 7 d of admission. Among secondary diagnosis patients, 19.8% died with 3 d of admission, and 29.8% died within 7 d of admission. Although the majority of patients were male, females and males had similar mortality rates (50% of mortalities were male). There were apparent racial/ethnic distributional differences, with non-Hispanic Whites being the only group that comprised a smaller proportion of the mortalities than the surviving cases.

Early intervention with pharmaceuticals was more frequent among mortality cases (Table 2). Receipt of PPI on the first or second day of admission occurred in 53.83% of patients, with higher usage among mortalities (68.56% *vs* 53.31%). H2RA were administered on the first or second day of admission in 20.57% of patients, with higher usage in mortality than non-mortality cases (37.62% *vs* 20.20%). Octreotide was only used in 4.04% of patients; 19.80% of patients who died received octreotide on the first or second day of admission, and 3.70% surviving cases received octreotide. Vasopressin was only given to 0.80% of patients; 24.50% of the mortality cases and 0.30% of surviving cases received vasopressin on the first or second day of admission.

Table 3 displays the top admitting diagnosis codes for mortalities and non-mortalities. Mortalities included several diagnosis codes not related to GI symptoms, including dyspnea and respiratory abnormalities, cardiac arrest, pneumonia, diseases of white blood cells, and respiratory failure. Non-mortalities more frequently carried GI-specific admitting diagnoses.

***Multivariable analysis***

**Factors associated with mortality in all GIB diagnoses:** After adjustment for other covariates, race was not significantly associated with mortality in patients with a primary diagnosis of UGIB or unspecified GIB (adjusted *P* = 0.999). Although the majority of patients were male, mortality tended to be higher in females; however, gender was not significantly associated with mortality (adjusted *P* = 0.339). Age was also not significantly associated with mortality (adjusted *P* = 0.999). These covariates were retained in the model for their role as potential confounders. Urban *vs* rural zip code of residence, H2RA within the first or second day of admission, and the interaction between endoscopy and chronic liver disease were not statistically significant and did not improve fit, thus were removed from the model [*χ2*(4) = 4.505, *P* = 0.342]. Furthermore, chronic liver disease, and the interaction between endoscopy and CCCs were not significant and did not significantly improve model fit and were also removed from the final model [*χ2* (3) = 4.612 *P* = 0.203]. Although PPI on the first or second day of the encounter was not significant after correcting for multiple testing, the inclusion of this variable significantly improved model fit [χ2 (1) = 5.451, *P* = 0.020].

Those patients who died were far less likely to have undergone an endoscopic procedure (OR = 0.489, 95%CI: 0.356-0.672; *P* < 0.0001), indicating a protective association with endoscopy. Mortalities were also less likely to have a GIB documented as present on admission (OR = 0.464, 95%CI: 0.362-0.596; *P* < 0.0001), and less likely to have had the GIB as the principal diagnosis for the encounter (OR = 0.266 95%CI: 0.165-0.429; *P* < 0.0001). This may suggest that GIB more commonly complicates inpatient stays for patients admitted or being primarily treated for other conditions. PPI administration on the first or second day of admission tended to be protective; however, the effect was not statistically significant after correction for multiple testing (OR = 0.723, 95%CI: 0.552-0.947; *P* = 0.074).

The odds of having 1 or 2 CCCs compared to 0 CCCs were 9.090 times higher for mortalities over non-mortalities (95%CI: 4.907-16.841; *P* < 0.0001), and the odds of having 3 or more CCCs compared to 0 CCCs was 27.338 (95%CI: 14.940-50.027; *P* < 0.0001) times higher for mortalities over non-mortalities. Mortalities have significantly increased odds of having multiple complex chronic conditions. Table 4 differentiates the presence of concomitant CCC in patients with GI bleeding as principal as opposed to secondary diagnosis whereas Table 5 summarizes the distribution of CCCs between mortality and non-mortality patients.

Mortalities had significantly higher odds of perforation as well (OR = 5.505, 95%CI: 1.717-17.650; *P* = 0.021). There was a significant association between mortality and diagnosis of sepsis during the encounter and mortality (OR = 2.583, 95%CI: 1.823-3.659; *P* < 0.0001). Mortalities had substantially higher odds of shock (OR = 3.585, 95%CI: 2.489-5.163; *P* < 0.0001), but this effect was modified by vasopressin. Mortalities had 4.834 times the odds of experiencing shock and receiving vasopressin compared to shock alone over non-mortalities (95%CI: 2.729-8.562; *P* < 0.0001). Vasopressin is primarily used to treat shock in critically ill children[3]. Higher mortality in patients receiving vasopressin and shock does not necessarily represent a causal chain - it may merely be highlighting the pattern that severe cases of shock were more frequently given vasopressin. The strength of the association is striking and the administration of vasopressin in shock cases did not associate with significantly improved outcomes. The effect of vasopressin on GI bleeds and shock warrants further investigation in pediatric patients.

Receiving octreotide or vasopressin was significantly associated with having a portal hypertension diagnosis [*χ2* (1) = 3261.5, *p* < 0.0001], and with having varices with bleeding [*χ2* (1) = 2477.2, *p* < 0.0001]. Receiving octreotide within the first 24 h was associated with a 2.934fold increase in odds of death (OR = 2.936, 95%CI: 1.981-4.351; *P* < 0.0001). This is more likely an indicator of severity of illness and early treatment as more severe patients who would eventually expire received more aggressive treatment.

**Factors affecting mortality in GIB as principal, admitting or present on admit:** As a sensitivity analysis, we isolated only those patients whose principal diagnosis was a GIB, or the GIB was present on admit or the admitting diagnosis to see if the trends observed associations pertained to a more refined group of GIB patients (*n* = 15539, 185 mortalities). After applying the model-fitting procedure, the final model yielded results similar to those observed for the full cohort of GIB patients in PHIS, with most of the associations being strengthened (the exception being CCCs), suggesting the secondary GIB may have biased estimates toward the null Age, race, and gender were not statistically significantly associated with mortality when controlling for other covariates (*P* = 0.999; *P* = 0.999; *P* = 0.937, respectively). Again, residing in an urban area, administration of H2RA on day 0 or 1, chronic liver disease, and the interaction between endoscopy and chronic liver disease were not significant and did not improve model fit [*χ2* (5) = 4.527, *P* = 0.476]. Perforation-type injury and GIB present on admission were not significant and subsequently removed from the final model [*χ2*(2) = 3.644, *P* = 0.162].

In this smaller cohort, patients who died were even less likely to have undergone an endoscopic procedure (OR = 0.327, 95%CI: 0.202-0.539; *P* < 0.0001). Mortalities had marginally lower odds of receipt of a PPI on the first or second day of admission (OR 0.613, 95% CI (0.417, 0.902); *P*=0.051). Receiving octreotide on the first or second day of admission was associated with an increase in odds of death (OR = 2.219, 95%CI: 1.286-3.831; *P* = 0.025).

The strength of the association with CCCs was not quite as pronounced in the smaller cohort. The odds of having 1 or 2 CCCs compared to 0 CCCs were 8.710 times higher for mortalities over non-mortalities (95%CI: 3.861-19.651; *P* < 0.0001), and the odds of having 3 or more CCCs compared to 0 CCCs was 24.098 (95%CI: 10.778-53.884; *P* < 0.0001) times higher for mortalities over non-mortalities. Mortalities have significantly increased odds of having multiple complex chronic conditions in the smaller cohort, but the associations are less strong.

There was a significant association between mortality and diagnosis of sepsis during the encounter (OR = 2.040, 95%CI: 1.197-3.477; *P* = 0.044). Mortalities had substantially higher odds of shock (OR = 5.426, 95%CI: 3.212-9.168; *P* < 0.0001) but this effect was modified by vasopressin, with a stronger association marked in the smaller cohort. Mortalities had 12.090 times the odds of experiencing shock and receiving vasopressin compared to shock alone over non-mortalities (95%CI: 5.327-27.442; *P* < 0.001).

**Factors associating with endoscopy:** In a separate model, we examined the association between various patient characteristics and whether or not the patient underwent endoscopy. A total of 5939 patients received endoscopy. Supplementary Table 2 stratifies therapeutic endoscopy type. The vast majority of endoscopic procedures were EGD. We adjusted the model for those factors relating to mortality and severity (shock, sepsis, packed red blood cell transfusion, GIB diagnosis present on admit, and GIB diagnosis as principal diagnosis). We found that those patients with chronic liver conditions were more likely to undergo endoscopy (OR = 2.378, 95%CI: 1.970-2.869; *P* < 0.0001), which may explain partially why this factor was not found significant in the mortality model. If endoscopy is protective and patients with chronic liver disease are more likely to undergo endoscopy, it stands to reason that they will then be less likely to die. We also found that living in a rural area was positively associated with endoscopy compared to living in an urban area (OR = 1.196, 95%CI: 1.076-1.329; *P* = 0.007). Compared to non-Hispanic white patients, Hispanics were 18.5% less likely to have undergone an endoscopic procedure (OR = 0.815, 95%CI: 0.737-0.900; *P* = 0.001). Age was also significantly associated with endoscopy, with a 6.39% increase in odds for every additional year (OR = 1.064, 95%CI: 1.058-1.070; *P* < 0.0001). Patients with 1 or 2 CCCs did not have increased odds of endoscopy (*P* = 0.999), but those with 3 or more had a 24.53% reduction in the odds of endoscopy (OR = 0.755, 95%CI: 0.686-0.830; *P* < 0.0001). Perforation injuries were also far less likely to undergo endoscopy (OR = 0.169, 95%CI: 0.116-0.247). GIBs as the principal diagnosis were associated with higher odds of endoscopy (OR = 2.626, 95%CI: 2.448-2.817; *P* < 0.0001). Those who underwent endoscopy were more likely to have experienced shock (OR = 1.752, 95%CI: 1.409-2.179; *P* < 0.0001), but less likely to have become septic (OR = 0.473, 95%CI: 0.370-0.604; *P* < 0.0001).

**DISCUSSION**

This is the first study describing the demographic and clinical characteristics of pediatric patients with GI hemorrhage in tertiary referral pediatric centers. In our cohort more than 75% of patients with GIB presented with hematemesis or blood in the stool. Mortality at, or before 3 days was more likely in patients with GIB as a primary diagnosis, and in this subgroup mortality was highest in the first 7 d of admission. The mortality in patients with a principal diagnosis of GIB was 0.37% whereas the mortality in patients with GIB as a secondary diagnosis was 2.96% signalling that GIB can be a terminal event in children with other severe disease processes.

We also found that in pediatric patients, race, gender, and age were not significantly associated with mortality. Death was most strongly associated with shock, sepsis, multiple complex chronic conditions and use of vasopressin and octreotide, although these pharmaceutical treatments may represent aggressive treatment of haemorrhage (octreotide) or hemodynamic support (vasopressin) for severely ill patients.

Our observations in children are analogous to published studies in adults showing mortality to be many times higher for upper GIB complicating the inpatient course in the presence of comorbidities[14]. In our cohort, we could not determine whether the increased mortality in patients with multiple chronic comorbidities was related to the GIB event or was intrinsic to the medical frailty of these patients. However, we observed the association to be consistent between both patients with any diagnosis of GIB as well as the more focused group with primary GIB diagnosis. GIB patients with multiple chronic illnesses are at incremental risk, and mortality in patients with primary GIB is significantly associated, albeit less robustly, with multiple complex chronic conditions than children with a secondary diagnosis. More specifically, our observations support the validity of the Sheffield Scoring System which identifies significant pre-existing condition as an independent determinant of the need for therapeutic endoscopy[11].

The observed increased mortality associated with GIB with chronic comorbidities and infection can be explained through several mechanisms. For example, the strong relationship between sepsis and mortality with GIB may relate to the development of disseminated intravascular coagulation that would exacerbate bleeding. Conversely septicemia may be a terminal complication in a child with multi-organ injury from bleeding-hypovolemic shock. Similarly oncologic comorbidities signal a greater degree of overall debility as a function of immunosuppression, impaired fluid and electrolyte balance, poor nutrition, suppressed erythropoiesis and several potential iatrogenic factors impacting homeostatic responses.

We could not, in this analysis, confirm a relationship between GIB related admission mortality and distance travelled to care as defined by rural compared with urban address; a significant relationship was noted when analysis was performed looking at all GIB associated mortality, this was not borne out when the cohort was defined by admitting or principal diagnosis.

Endoscopy was associated with lower mortality, as was the administration of a PPI on the first or second day of admission. Mortality was also lower for patients with GIB that was present on admission or the principal diagnosis, supporting the impression that GIB can be viewed as an ominous complication defining a generally more dismal outcome in children.

We did find that certain patients were more likely to undergo endoscopy. Endoscopy during admission with GIB diagnosis was significantly protective (OR = 0.49); the effect was most pronounced in children with a principal diagnosis of GIB (OR = 0.28). Chronic liver disease patients were much more likely to undergo endoscopy, which may explain why this comorbidity, in turn, was not found to be significantly associated with mortality although it is a known risk factor. Racial and urban *vs* rural differences were also noted. Hispanics were significantly less likely to undergo endoscopy during admission with GIB and mortality with GIB is lowest in non-Hispanic white children.

The sensitivity analysis yielded similar results when we focused on a smaller cohort of patients with principal diagnosis of GIB, admitting diagnosis of GIB, or GIB present on admit. The purpose of examining the smaller cohort was to exclude as much as possible those secondary GIB cases that arose as complication of a non-GIB disease course. We found even stronger association for most of the covariates, suggesting possible masking and bias toward the null by including more complex and severely ill patients whose hospital stay was not chiefly attributed to a GIB.

As a retrospective observational study using primarily administrative billing data, there are several limitations to the study. The use of ICD-9 diagnosis codes has been shown to be sensitive and specific for some conditions and procedures including gastrointestinal hemorrhage[15] but are unknown for all ICD-9 codes. Coding practices may also vary within hospitals, and the reliability of these codes depends on proper documentation. Substantial risk factors or severity factors may be missing from the data.

In summary, we have reported on the mortality associated with admission for acute GI hemorrhage in children. Gastrointestinal hemorrhage can be fatal but more often defines deterioration in a child with other, especially multiple, comorbidities. Intense pharmacologic support associates with mortality underscoring the escalation of therapy with increased clinical compromise. Endoscopy was consistently protective from mortality, and the timing, scope and therapeutic goals of endoscopy in GI hemorrhage are still to be precisely defined and universally applied in children. Emerging scoring systems and prospective implementation of such may go some way to identifying and stratifying the protective effects of endoscopy in children. This study offers new impetus to aggressive, including endoscopic, management.

**COMMENTS**

***Background***

The presentation, course and outcome of gastrointestinal haemorrhage in children compared with adults remains poorly characterized; little is known about factors related mortality associated with gastrointestinal bleeding in children and this impedes an evidence based approach to management in this population.

***Research frontiers***

Upper gastrointestinal haemorrhage, younger age at presentation and multiple comorbidities are associated with admission, whereas chronic illness, need for transfusion and large haemoglobin drop signal the need for endoscopy during admission. Mortality with GI haemorrhage is most frequently associated with esophageal or intestinal perforation.

***Innovations and breakthrough***

gastrointestinal haemorrhage in children resulting in admission is associated with chronic comorbidities, most notably gastrointestinal, liver and cardiovascular disorders. Mortality is greater with more comorbid conditions at admission and more aggressive pharmacologic intervention whereas endoscopy during the admission was protective.

***Applications***

the prognosis for patients with gastrointestinal haemorrhage complicating the inpatient course especially in children with sepsis or multiple chronic comorbidities and requiring more aggressive hemodynamic support is especially guarded.

***Peer-review***

This manuscript is a very well designed and conducted retrospective study. There are outstanding information for clinical practice and important clues for prospective trials.

**References**

1 **Lirio RA**. Management of Upper Gastrointestinal Bleeding in Children: Variceal and Nonvariceal. *Gastrointest Endosc Clin N Am* 2016; **26**: 63-73 [PMID: 26616897]

2 **Thomson M**, Belsha D. Endoscopic management of acute gastrointestinal bleeding in children: Time for a radical rethink. *J Pediatr Surg* 2016; **51**: 206-210 [PMID: 26703435]

3 **Lanas A**, García-Rodríguez LA, Polo-Tomás M, Ponce M, Alonso-Abreu I, Perez-Aisa MA, Perez-Gisbert J, Bujanda L, Castro M, Muñoz M, Rodrigo L, Calvet X, Del-Pino D, Garcia S. Time trends and impact of upper and lower gastrointestinal bleeding and perforation in clinical practice. *Am J Gastroenterol* 2009; **104**: 1633-1641 [PMID: 19574968]

4 **Hernández-Díaz S**, Rodríguez LA. Incidence of serious upper gastrointestinal bleeding/perforation in the general population: review of epidemiologic studies. *J Clin Epidemiol* 2002; **55**: 157-163 [PMID: 11809354]

5 **Pant C**, Olyaee M, Sferra TJ, Gilroy R, Almadhoun O, Deshpande A. Emergency department visits for gastrointestinal bleeding in children: results from the Nationwide Emergency Department Sample 2006-2011. *Curr Med Res Opin* 2015; **31**: 347-351 [PMID: 25466210 DOI: 10.1185/03007995.2014.986569]

6 **Pant C**, Sankararaman S, Deshpande A, Olyaee M, Anderson MP, Sferra TJ. Gastrointestinal bleeding in hospitalized children in the United States. *Curr Med Res Opin* 2014; **30**: 1065-1069 [PMID: 24450577]

7 **Tielleman T**, Bujanda D, Cryer B. Epidemiology and Risk Factors for Upper Gastrointestinal Bleeding. *Gastrointest Endosc Clin N Am* 2015; **25**: 415-428 [PMID: 26142028]

8 **Rockall TA**, Logan RF, Devlin HB, Northfield TC. Risk assessment after acute upper gastrointestinal haemorrhage. *Gut* 1996; **38**: 316-321 [PMID: 8675081]

9 **Provenzale D**, Sandler RS, Wood DR, Levinson SL, Frakes JT, Sartor RB, Jackson AL, Kinard HB, Wagner EH, Powell DW. Development of a scoring system to predict mortality from upper gastrointestinal bleeding. *Am J Med Sci* 1987; **294**: 26-32 [PMID: 3496791]

10 **Pimpl W**, Boeckl O, Waclawiczek HW, Heinerman M. Estimation of the mortality rate of patients with severe gastroduodenal hemorrhage with the aid of a new scoring system. *Endoscopy* 1987; **19**: 101-106 [PMID: 3497027 DOI: 10.1055/s-2007-1013010]

11 **Thomson MA**, Leton N, Belsha D. Acute upper gastrointestinal bleeding in childhood: development of the Sheffield scoring system to predict need for endoscopic therapy. *J Pediatr Gastroenterol Nutr* 2015; **60**: 632-636 [PMID: 25539193 DOI: 10.1097/MPG.0000000000000680]

12 **Feudtner C**, Feinstein JA, Zhong W, Hall M, Dai D. Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation. *BMC Pediatr* 2014; **14**: 199 [PMID: 25102958 DOI: 10.1186/1471-2431-14-199]

13 **Feudtner C**, Villareale NL, Morray B, Sharp V, Hays RM, Neff JM. Technology-dependency among patients discharged from a children's hospital: a retrospective cohort study. *BMC Pediatr* 2005; **5**: 8 [PMID: 15882452 DOI: 10.1186/1471-2431-5-8]

14 **Scottish Intercollegiate Guidelines Network**. Management of Acute Upper and Lower Gastrointestinal Bleeding - A National Clinical Guideline. Scottish Intercoll Guidel Netw [Internet]. 2008: 1-56 Available from: URL: <http://www.sign.ac.uk/guidelines/fulltext/105/index.htm>

15 **Valkhoff VE**, Coloma PM, Masclee GM, Gini R, Innocenti F, Lapi F, Molokhia M, Mosseveld M, Nielsson MS, Schuemie M, Thiessard F, van der Lei J, Sturkenboom MC, Trifirò G. Validation study in four health-care databases: upper gastrointestinal bleeding misclassification affects precision but not magnitude of drug-related upper gastrointestinal bleeding risk. *J Clin Epidemiol* 2014; **67**: 921-931 [PMID: 24794575 DOI: 10.1016/j.jclinepi.2014.02.020]

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**Table 1 Patient characteristics by principal and secondary diagnosis of gastrointestinal bleeding *n* (**%**)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **GI bleed is(N=6733)****is GI Bleed is (N=12795)** | **Overall (*n* = 19528)** | ***P* value** |
| **Principal Dx** | **Secondary Dx** |
| Age in years (IQR) | 10 (4, 15) | 9 (4, 15) | 9 (4, 15) | < 0.0001 |
| Gender |  |  |  | < 0.0001 |
| Female | 2925 (43.44) | 5941 (46.43) | 8866 (45.40) |  |
| Male | 3808 (56.56) | 6854 (53.57) | 10762 (55.11) |  |
| Race |  |  |  | < 0.0001 |
| Non-Hispanic White | 3608 (53.59) | 6596 (51.55) | 10204 (52.25) |  |
| Non-Hispanic Black | 1180 (17.53) | 2257 (17.64) | 3437 (17.60) |  |
| Hispanic | 1159 (17.21) | 2580 (20.16) | 3739 (19.15) |  |
| Asian | 251 (3.73) | 332 (2.59) | 583 (2.99) |  |
| Other | 412 (6.12) | 779 (6.09) | 1191 (6.10) |  |
| Unknown | 123 (1.83) | 251 (1.96) | 374 (1.92) |  |
| Urban/rural |  |  |  | 0.1247 |
| Urban | 5730 (85.10) | 10930 (85.42) | 16660 (85.31) |  |
| Rural | 873 (12.97) | 1573 (12.29) | 2446 (12.53) |  |
| Unknown | 130 (1.93) | 292 (2.28) | 422 (2.16) |  |
| Complex chronic Conditions |  |  |  | < 0.0001 |
| 0 | 3767 (55.95) | 5969 (46.65) | 9736 (49.86) |  |
| 1-2 | 1771 (26.30) | 4328 (33.83) | 6099 (31.23) |  |
| ≥ 3 | 1195 (17.75) | 2498 (19.52) | 3693 (18.91) |  |
| GIH symptoms |  |  |  |  |
| Hematemesis | 2333 (34.65) | 4263 (33.32) | 6596 (33.78) | 0.0635 |
| Melena | 1983 (29.45) | 6018 (47.03) | 8001 (40.97) | < 0.0001 |
| Hypovolemia | 52 (0.77) | 90 (0.70) | 142 (0.73) | 0.5956 |
| Pharmaceutical Interventions |  |  |  |  |
| PPI on day 0 or 1 | 4473 (66.43) | 6038 (47.19) | 10511 (53.83) | < 0.0001 |
| H2RA on day 0 or 1 | 1301 (19.32) | 2715 (21.22) | 4016 (20.57) | 0.0019 |
| Erythromycin on day 0 or 1 | 197 (2.93) | 313 (2.45) | 510 (2.61) | 0.0511 |
| Vasopressin on day 0 or 1 | 15 (0.22) | 142 (1.11) | 157 (0.80) | < 0.0001 |
| Octreotide on day 0 or 1 | 349 (5.18) | 439 (3.43) | 788 (4.04) | < 0.0001 |
| Diagnostic Imaging |  |  |  |  |
| Meckel's Scan day 0-2 | 497 (7.38) | 378 (2.95) | 875 (4.48) | < 0.0001 |
| Abdomen CT day 0-2 | 425 (6.31) | 1298 (10.14) | 1723 (8.82) | < 0.0001 |
| Abdomen MRI day 0-2 | 44 (0.65) | 170 (1.33) | 214 (1.10) | < 0.0001 |
| Arteriography day 0-2 | 75 (1.11) | 93 (0.73) | 168 (0.86) | 0.0070 |
| Surgical Interventions |  |  |  |  |
| Laparotomy, Exploratory | 23 (0.34) | 44 (0.34) | 67 (0.34) | 0.9999 |
| Laparotomy, Other | 2 (0.03) | 19 (0.15) | 21 (0.11) | 0.0191 |
| Laparoscopy | 54 (0.80) | 96 (0.75) | 150 (0.77) | 0.7303 |
| Esophagogastroduodenoscopy | 2304 (34.22) | 2317 (18.11) | 4621 (23.66) | < 0.0001 |
| Other Endoscopy | 845 (12.55) | 845 (6.6) | 1690 (8.65) | < 0.0001 |
| Transcatheter embolization | 8 (0.12) | 8 (0.06) | 16 (0.08) | 0.1977 |
| Ligation, esophag. varices | 0 (0.0) | 5 (0.04) | 5 (0.03) | 0.1719 |
| Ligation, gastric varices | 1 (0.01) | 5 (0.04) | 6 (0.03) | 0.6713 |
| Packed red blood cell Transfusions | 1265 (18.79) | 2337 (18.26) | 3602 (18.45) | 0.3808 |
| Platelet transfusions | 194 (2.88) | 799 (6.24) | 993 (5.09) | <0.001 |
| ICU stay as part of encounter | 880 (13.07) | 2328 (18.19) | 3208 (16.43) | <0.0001 |
| Chronic liver disease | 171 (2.54) | 400 (3.13) | 571 (2.92) | 0.0234 |
| GIH Present on admit | 4980 (73.96) | 8585 (67.10) | 11084 (56.76%) | <0.0001 |
| Shock | 144 (2.14) | 584 (4.56) | 728 (3.73) | <0.0001 |
| Sepsis | 30 (0.45) | 666 (5.21) | 696 (3.56) | <0.0001 |
| Hospital lOS (IQR) | 2 (1, 4) | 3 (2, 7) | 3 (1, 6) | < 0.0001 |
| Day of EGD | 1 (0, 2) | 2 (1, 3) | 1 (0, 2) | < 0.0001 |
| Mortality | 25 (0.37) | 379 (2.96) | 404 (2.07) | < 0.0001 |

**Table 2 Univariate analysis of factors affecting mortality *n* (**%**)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Survived****(N=19124)** | **Died**  **(N=404)** | **Overall(N=19528)** | ***P* value** |
| Age in years (IQR) | 9 (4, 15) | 8 (3, 15) | 9 (4, 15) | 0.2997 |
| Gender |  |  |  | 0.0679 |
| Female | 8864 (46.35) | 202 (50) | 9066 (46.43) |  |
| Male | 10460 (54.70) | 202 (50) | 10662 (54.60) |  |
| Race |  |  |  | 0.0005 |
| Non-Hispanic White | 10036 (52.48) | 168 (41.58) | 10204 (52.25) |  |
| Non-Hispanic Black | 3358 (17.56) | 79 (19.55) | 3437 (17.60) |  |
| Hispanic | 3646 (19.07) | 93 (23.02) | 3739 (19.15) |  |
| Asian | 565 (2.95) | 18 (4.46) | 583 (2.99) |  |
| Other | 1156 (6.04) | 35 (8.66) | 1191 (6.10) |  |
| Unknown | 363 (1.90) | 11 (2.72) | 374 (1.92) |  |
| Urban/rural |  |  |  | 0.2524 |
| Urban | 16324 (85.36) | 336 (83.17) | 16660 (85.31) |  |
| Rural | 2385 (12.47) | 61 (15.10) | 2446 (12.53) |  |
| Unknown | 415 (2.17) | 7 (1.73) | 422 (2.16) |  |
| Complex chronic conditions | < 0.0001 |
| 0 | 9689 (50.66) | 12 (2.97) | 9701 (49.68) |  |
| 1-2 | 5825 (30.46) | 95 (23.51) | 5920 (30.32) |  |
| ≥ 3 | 3610 (18.88) | 297 (73.51) | 3907 (20.01) |  |
| GIH symptoms |  |  |  |  |
| Hematemesis | 6508 (34.03) | 88 (21.78) | 6596 (33.78) | < 0.0001 |
| Melena | 7899 (41.30) | 102 (25.25) | 8001 (40.97) | < 0.0001 |
| Hypovolemia | 131 (0.69) | 11 (2.72) | 142 (0.73) | 0.0002 |
| GER | 2329 (12.18) | 50 (12.38) | 2379 (12.18) | 0.9653 |
| Pharmaceutical interventions |
| PPI first 24 h | 10234 (53.51) | 277 (68.56) | 10511 (53.83) | < 0.0001 |
| H2RA first 24 h | 3864 (20.20) | 152 (37.62) | 4016 (20.57) | < 0.0001 |
| Erythromycin first 24 h | 480 (2.51) | 30 (7.43) | 510 (2.61) | < 0.0001 |
| Vasopressin first 24 h | 58 (0.30) | 99 (24.50) | 157 (0.80) | < 0.0001 |
| Octreotide first 24 h  | 708 (3.70) | 80 (19.80) | 788 (4.04) | < 0.0001 |
| Surgical interventions |
| Laparotomy, exploratory | 54 (0.28) | 13 (3.22) | 67 (0.34) | < 0.0001 |
| Laparotomy, other | 16 (0.08) | 5 (1.24) | 21 (0.11) | < 0.0001 |
| Laparoscopy | 144 (0.75) | 6 (1.49) | 150 (0.77) | 0.1347 |
| Esophagogastroduodenoscopy | 4569 (23.89) | 52 (12.87) | 4621 (23.66) | < 0.0001 |
| Other Endoscopy | 1638 (8.57) | 52 (12.87) | 1690 (8.65) | 0.0031 |
| Transcatheter embolization | 14 (0.07) | 2 (0.50) | 16 (0.08) | 0.0423 |
| Ligation, esophag. varices | 4 (0.02%) | 1 (0.25%) | 5 (0.03) | 0.0993 |
| Ligation, gastric varices | 6 (0.03) | 0 (0.00) | 6 (0.03) | 0.9999 |
| Diagnostic imaging |
| Meckel's Scan day 0-2 | 873 (4.56) | 2 (0.50) | 875 (4.48) | 0.0001 |
| Abdomen CT day 0-2 | 1675 (8.76) | 48 (11.88) | 1723 (8.82) | 0.0356 |
| Abdomen MRI day 0-2 | 212 (1.11) | 2 (0.50) | 214 (1.10) | 0.3340 |
| Arteriography day 0-2 | 163 (0.85) | 5 (1.24) | 168 (0.86) | 0.4031 |
| Packed red blood cell Transfusion | 3361 (17.57) | 241 (59.65) | 3602 (18.45) | < 0.0001 |
| Platelet transfusion | 819 (4.28) | 174 (43.07) | 993 (5.09) | < 0.0001 |
| ICU stay as part of encounter | 2863 (14.97) | 345 (85.40) | 3208 (16.43) | < 0.0001 |
| Chronic liver disease | 536 (2.80) | 35 (8.66) | 571 (2.92) | < 0.0001 |
| GIB Present on admit | 13386 (70.00) | 179 (44.31) | 11084 (56.76) | < 0.0001 |
| Principal Dx GIB | 6708 (35.07) | 25 (6.18) | 6733 (34.48) | < 0.0001 |
| Sepsis | 516 (2.70) | 180 (44.55) | 696 (3.56) | < 0.0001 |
| Shock | 562 (2.94) | 166 (41.09) | 728 (3.73) | < 0.0001 |
| Hospital LOS (IQR) | 3 (1, 6) | 19 (5, 49) | 3 (1, 6) | < 0.0001 |
| Day of EGD | 1 (0, 2) | 3 (1, 14) | 1 (0, 2) | <0.0001 |

**Table 3 Top 10 admitting diagnoses for mortalities and non-mortalities**

|  |  |  |
| --- | --- | --- |
| **ICD-9 code** | **ICD-9 code description** | ***n* (%)** |
| Mortalities |  |  |
| 780.60 | Fever | 32 (7.92) |
| 786.09 | Other dyspnea and respiratory abnormality | 23 (5.69) |
| 787.03 | Vomiting alone | 15 (3.71) |
| 03.89 | Unspecified septicemia | 14 (3.47) |
| 578.0 | Hematemesis | 13 (3.22) |
| 427.5 | Cardiac arrest | 13 (3.22) |
| 578.9 | Hemorrhage of GI tract, unspecified | 12 (2.97) |
| 486.0 | Pneumonia, organism unspecified | 11 (2.72) |
| 288.00 | Diseases of white blood cells | 10 (2.48) |
| 518.81 | Acute respiratory failure | 10 (2.48) |
| Non-mortalities |  |  |
| 578.0 | Hematemesis | 3058 (15.99) |
| 578.1 | Blood in Stool | 2750 (14.38) |
| 578.9 | Hemorrhage of GI tract, unspecified | 1289 (6.74) |
| 789.00 | Other symptoms involving abdomen and pelvis | 755 (3.95) |
| 787.03 | Vomiting alone | 748 (3.91) |
| N/A | Not available or Missing | 707 (3.70) |
| 780.60 | Fever | 559 (2.92) |
| 276.51 | Dehydration | 515 (2.69) |
| 787.91 | Diarrhea | 500 (2.61) |
| 2859 | Anemia | 292 (1.53) |

**Table 4 Complex chronic conditions by principal and secondary diagnosis of gastrointestinal bleeding *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Principal Dx is GI bleed (*n* = 4521)** | **Secondary Dx is GI bleed (*n* = 15007)** | ***P* value** |
| GI flag | 1681 (24.39) | 3892 (15.39) | < 0.0001 |
| Cardiovascular flag | 513 (7.44) | 1192 (4.71) | < 0.0001 |
| Hem/immunologic flag | 422 (6.12) | 1392 (5.5) | < 0.0001 |
| Malignancy | 284 (4.12) | 1015 (4.01) | < 0.0001 |
| Metabolic flag | 258 (3.74) | 1015 (4.01) | < 0.0001 |
| Neurologic/neuromusc flag | 972 (14.1) | 1743 (6.89) | 0.1234 |
| Congenital/genetic flag | 727 (10.55) | 1192 (4.71) | 0.0010 |
| Renal/urologic flag | 249 (3.61) | 811 (3.21) | < 0.0001 |
| Respiratory flag | 244 (3.54) | 601 (2.38) | 0.0005 |
| Technology depend. flag | 1353 (19.63) | 2599 (10.28) | 0.7331 |
| Transplant flag | 318 (4.61) | 578 (2.29) | 0.5374 |

GI: gastrointestinal.

**Table 5 Complex chronic conditions by discharge disposition *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Survived (*n* = 19124)** | **Died (*n* = 404)** | ***P* value** |
| gastrointestinal flag | 5351 (27.98) | 159 (39.36) | < 0.0001 |
| Cardiovascular flag | 1543 (8.07) | 162 (40.10) | < 0.0001 |
| Hem/immunologic flag | 1662 (8.69) | 152 (37.62) | < 0.0001 |
| Malignancy | 1164 (6.09) | 135 (33.42) | < 0.0001 |
| Metabolic flag | 1138 (5.95) | 135 (33.42) | < 0.0001 |
| Neurologic/neuromusc flag | 2570 (13.44) | 145 (35.89) | < 0.0001 |
| Congenital/genetic flag | 1838 (9.61) | 81 (20.05) | < 0.0001 |
| Renal/urologic flag | 927 (4.85) | 133 (32.92) | < 0.0001 |
| Respiratory flag | 780 (4.08) | 65 (16.09) | < 0.0001 |
| Technology depend. flag | 3710 (19.40) | 242 (59.90) | < 0.0001 |
| Transplant flag | 802 (4.19) | 94 (23.27) | < 0.0001 |