Why do mortality rates for nonvariceal upper gastrointestinal bleeding differ around the world? A systematic review of cohort studies

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BACKGROUND: Discrepancies exist in reported mortality rates of nonvariceal upper gastrointestinal bleeding (NVUGIB).
OBJECTIVE: To perform a systematic review assessing possible reasons for these disparate findings and to more reliably compare them.
METHODS: The MEDLINE, EMBASE and ISI Web of Knowledge databases were searched for studies reporting mortality rates in NVUGIB involving adults and published in English. To ensure robust and contemporary estimates, studies spanning 1996 to January 2011 that included more than 1000 patients were selected.
RESULTS: Eighteen of 3077 studies were selected. Ten studies used administrative databases and the remaining eight used registries. The mortality rates reported in these studies ranged from 1.1% in Japan to 11% in Denmark. There were variations in reported mortality rates among countries and also within countries. Reasons for these disparities included a spectrum of quality in reporting as well as heterogeneous definitions of case ascertainment, differing patient populations with regard to severity of presentation and associated comorbidities, varying durations of follow-up and different health care system-related practices.
CONCLUSIONS: Wide differences in reported NVUGIB mortality rates are attributable to differences in adopted methodologies and populations studied. More uniform standards in reporting are needed; only then can true observed variations enable a better understanding of causes of death and pave the way to improved patient outcomes.

Key Words: *Acetylsalicylic acid; Acute gastrointestinal bleeding; Bleeding peptic ulcer; Gastrointestinal endoscopy*

Pourquoi le taux de mortalité causée par les hémorragies œsogastroduodénales non variqueuses diffère-t-il de par le monde? Une analyse systématique d'études de cohorte

HISTORIQUE : Il existe des écarts dans les taux de mortalité déclarés d'hémorragies œsogastroduodénales non variqueuses (HOGDNV).
OBJECTIF : Effectuer une analyse systématique pour évaluer les raisons possibles de ces observations disparates et les comparer de manière plus fiable.
MÉTHODOLOGIE : Les chercheurs ont effectué des recherches dans les bases de données MEDLINE, EMBASE et ISI Web of Knowledge pour trouver des études publiées en anglais précisant le taux de mortalité causée par les HOGDNV chez des adultes. Afin de garantir des évaluations robustes et contemporaines, les chercheurs ont sélectionné des études de plus de 1 000 patients menées de 1996 à janvier 2011.
RÉSULTATS : Les chercheurs ont retenu 18 des 3 077 études. Dix études faisaient appel à des bases de données administratives et les huit autres, à des registres. Le taux de mortalité déclarée dans ces études variait entre 1,1 % au Japon et 11 % au Danemark. On constatait des variations dans le taux de mortalité déclarée entre les pays et également dans un même pays. Les raisons de ces disparités incluaient un spectre de qualité des déclarations et des définitions hétérogènes d'évaluation des cas, des populations de patients différentes à l'égard de la gravité de la présentation et des comorbidités connexes, des durées de suivi variées et des pratiques différentes liées aux systèmes de santé.
CONCLUSIONS : Les grandes différences de taux de mortalité causée par les HOGDNV sont attribuables aux diverses méthodologies adoptées et populations étudiées. Des normes de déclaration plus uniformes s'imposent. Ce n'est qu'alors que les véritables variations observées permettront de mieux comprendre les causes de décès et d'améliorer les issues des patients.

Nonvariceal upper gastrointestinal bleeding (NVUGIB) is a common problem worldwide, with reports of its incidence ranging from 48 to 160 cases per 100,000 adults per year (1-3). NVUGIB is associated with considerable morbidity, mortality and economic impact, despite significant advances in its management over the past two decades. In the past two years, several publications have focused on the epidemiology and changing time trends of acute NVUGIB. Most of these studies have reported a reduction in its incidence and associated case fatality (henceforth referred to as 'mortality') rate (4-8), although some have reported no changes in mortality (9-11). The reductions in mortality observed over time have been largely attributed to combinations of therapeutic endoscopy, proton pump inhibitors, eradication of *Helicobacter pylori*, preventive strategies in individuals taking nonsteroidal anti-inflammatory drugs and advances in critical care. Because most patients do not die from uncontrolled bleeding (12,13), further improvements in outcomes will be challenging in the face of an aging population with the associated burden of comorbidities. Several recent studies and reviews have served to highlight variations in mortality rates reported for NVUGIB, ranging from 3% to 12%, as well as highlighting substantial differences in mortality among countries (9,14-18). The studies reporting these outcomes range from prospectively collected national registries for NVUGIB to retrospective analyses of large administrative databases. Such marked differences in outcomes are surprising because most of these studies originate from health care systems with access to modern-day, evidence-based standards and processes of care for managing NVUGIB.

A range of factors can influence the survival of patients with NVUGIB including those related to patients, disease severity and health care systems. Comparisons among countries are fraught with difficulty due to the complexity and intricacy of factors influencing

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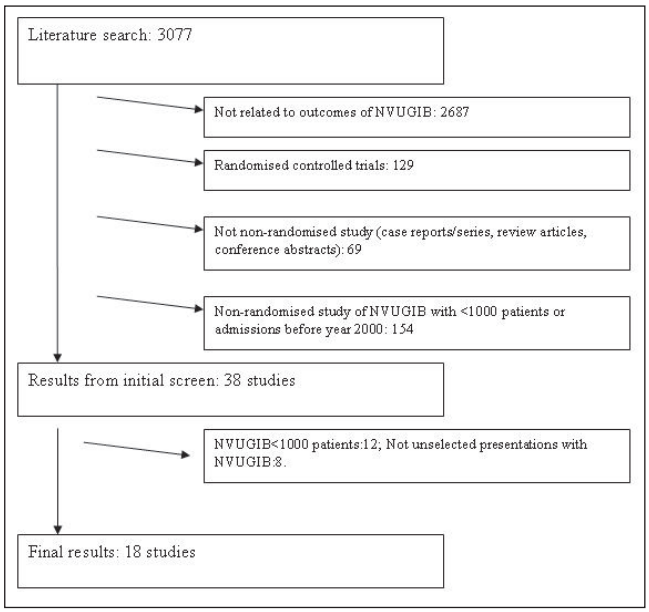

Figure 1) *Search results. NVUGIB Nonvariceal upper gastrointestinal bleeding*

mortality. We aimed to address possible reasons for the differences in reported mortality, and to more reliably compare current rates by systematically reviewing and appraising recent literature reporting mortality rates for acute NVUGIB, focusing on study methodology, source case ascertainment, reporting of key prognostic factors and quality of study reporting.

METHODS

Search strategy

The MEDLINE, EMBASE and ISI Web of Knowledge databases were searched for nonrandomized studies reporting mortality rates following presentation with NVUGIB. Search terms were combined with a highly sensitive observational study filter and restricted to include adult, human studies in English spanning 1996 to January 2011 (search terms can be provided on request). Reports preceding this period were not sought because of the significant evolution of general supportive care, and advances in endoscopic and pharmacological therapies that occurred during that time period (19); therefore, it was hypothesized that the chosen time period would represent a more homogenous group of data to compare. The bibliographies of identified articles were also screened.

Eligibility criteria

Cohort studies reporting mortality outcomes were searched for unselected patients presenting to hospital with acute NVUGIB. Only studies that reported outcomes for more than 1000 patients were included. For studies including both NVUGIB and acute variceal hemorrhage (AVH), only studies examining more than 1000 patients with NVUGIB were included. Studies published only as abstracts were excluded because they did not allow an adequate assessment of methodology. Citations identifed were screened in duplicate, with a kappa statistic of 0.65 (95% CI 0.60 to 0.70). Following the development of a data abstraction sheet, results were extracted by two reviewers (VJ, MM). Any disagreements were resolved by discussion and did not necessitate arbitration by a third person. Recorded information from each study included year of publication, study design, country of origin, nature of database analyzed, whether examining all-cause NVUGIB or a selected subgroup (eg, peptic ulcer bleeding only), age, new admission and/or inpatient bleeds, length of follow-up and mortality rate. Also assessed was the methodological quality of the study report, using criteria for the reporting of nonrandomized studies from the Cochrane Collaboration (20) and Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) criteria for reporting of cohort studies (21).

Data analysis

Because the main aim of the present study was to examine differences in mortality rates and to attempt to identify the sources responsible for the variations observed, and because of the heterogeneity of the studies, only descriptive individual study data, without an attempt at formal meta-analysis, are provided. Indeed, the underlying assumption was that the mortality rate attributable to NVUGIB was not uniform, but rather, that it is dependent on a number of factors that are raised and outlined.

RESULTS AND DISCUSSION

Search results

The search yielded a total of 3077 articles, of which 3039 were excluded at the initial screen based on the title and abstract. The remaining 38 articles were reviewed in full for eligibility against prespecified criteria. An additional 20 studies were excluded, leaving 18 (11,12,14,16-18,22-33) in the final review. Reasons for exclusion are described in Figure 1.

What are the reported mortality rates following NVUGIB?

The studies originated from Europe, Asia and North America (Table 1). The sources of data ranged from prospective cohort registries for peptic ulcer bleeding from single centres of expertise (12) to large retrospective cohorts from nationwide administrative data sets (14). Ten studies used administrative databases and the remaining eight used registries specifically designed to assess 'real-life' outcomes following NVUGIB, resulting in a mixture of retrospective and prospective cohort studies. The mortality rates reported in these studies ranged from 1.1% in Japan to 11% in Denmark. Not only was there variation in reported mortality among countries, there was notable variation reported within countries (Table 1).

Why might reported mortality rates differ?

Source of case ascertainment: Definitions of NVUGIB should be clear and consistent throughout studies to enable comparability. Completeness of case ascertainment and degree of population coverage will influence reported mortality. Three studies from Italy in the present review conducted over the same time period reported mortalities ranging from 2.6% to 6.9% (17,28,31). One study used administrative data (28) and the other two used registry data (17,31). All three studies examined NVUGIB but definitions varied: two studies were reliant on retrospectively collected data coded by *International Classification of Diseases, Ninth Revision* (ICD-9)-CM (28,31) discharge diagnoses including variations in the codes selected within each study, whereas the third study was a prospectively collated registry requiring confirmation of upper gastrointestinal tract bleeding by clinical examination by admitting medical/nursing personnel (17). Administrative databases, not designed for research, have the advantage of size and population-based longitudinal follow up, but accuracy of case ascertainment is dependent on coding. In addition, they are often unable to adjust for key disease-specific prognostic variables. Positive predictive values (PPVs) of ICD-9-CM coding for peptic ulcers and gastrointestinal bleeding have been shown to be reasonably accurate, with PPVs ranging from 85% to 95% (34), but differ depending on the terminology used (35-37). The terms with the greatest PPVs (>90%) were for site-specific codes (eg, 'gastric' or 'duodenal' ulcer), but these were lower for lesion-specific codes (ie, 'peptic ulcer') and even lower for nonspecific terms such as 'melena' or 'hematemesis' (34). In addition, coding errors have been demonstrated in up to 7% of cases (34), which may result in thousands of miscoded cases in large datasets. This was fittingly highlighted in an article by Ahsberg et al (18), who stated "we found a sudden increase in hospitalisations for ulcer UNS (unspecified) after 1997, and at the same time-point, there was a large drop in hospitalisations for bleeding and perforated ulcers. These changes

TABLE 1
Studies detailed according to preselected reporting characteristics that may influence observed mortality rates

Author (reference), year; year(s) of patient admission	Country	Patient population	Design	Patients included in analysis, n	New admissions only and/or inpatient bleeds	Length of follow-up	Mortality rate
Ahsberg et al (18), 2011; 1987–2005	Denmark	PUB; using ICD9CM and ICD10 discharge coding	RCS (National Hospital Discharge Register)	58,445	Not reported	30 days	6.2% (2004/2005) 5.3% (1987/1988); age/sex standardized
Ananathakhrishnan et al (14), 2009; not reported	USA	NVUGIH and AVH using ICD9CM discharge coding	RCS (Nationwide inpatient sample)	391,119	'Primary discharge diagnosis of UGIH'	In hospital	3.0% weekday, 3.3% weekend (data for NVUGIH)
Barkun et al (26), 2004; 1999–2001	Canada	NVUGIH hematemesis/ coffee ground/ hematochezia, witnessed by medical staff (only if underwent endoscopy)	PCS (Registry from 18 Canadian hospitals)	1869	New admissions with symptoms within proceeding 24 h	30 days	5.4%
Button et al (32), 2011; 1999–2007	Wales	UGIB; using ICD10 discharge codes	RCS (Patient Episode Database for Wales)	24,421	New admission and inpatients (if UGIB coded as principal diagnosis)	30 days	10.0%
Chiu et al (23), 2009; 1993–2003	Hong Kong	Peptic ulcers; consecutive patients with endoscopic stigmata of bleeding	PCS (single-centre [Prince of Wales Hospital*])	3220	New admissions only	In hospital	7.1%
Cooper et al (40), 2009; 2004	USA	NVUGIH >65 yrs, using ICD9CM coding	RCS (Medicare claims data)	9123	ICD9CM diagnosis of 'UGIH'	30 days	8.0% (inpatients) 6.3% (outpatients)
Dorn et al (27), 2009; 1998–2003	USA	UGIH; "principal diagnosis of UGIB, GI bleeding and upper GI tract disease"	RCS (Nationwide inpatient sample)	98,975	New admissions and inpatient bleeds	In hospital	3.8% (weekend), 3.3% (weekday)
Hearnshaw et al (16), 2010; 2007	UK	Acute upper GI bleeding; hematemesis/melena within previous 10 days	PCS (212 UK hospitals)	6750	New admission and inpatient bleeds	In hospital (within 30 days)	7.4% (in those undergoing endoscopy)
Kohn et al (28), 2009; 2000–2005	Italy	UGIH; primary diagnosis of UGIH using ICD	RCS (Regional hospital information system)	13,427	Primary diagnosis of UGIH using ICD	30 days	6.9%
Lanas et al (11), 2009; 1996–2005	Spain	NVUGIH; primary discharge diagnosis using ICD9CM coding	RCS (10 Spanish hospitals)	3828	'Primary discharge diagnosis' using ICD9CM coding	Hospital discharge	5.5% (for validated cases)
Marmo et al (17), 2008; 2003–2004	Italy	NVUGIH; within 24 h before admission or developed as inpatient	PCS (Registry from 23 Italian hospitals)	1020	New admissions and inpatient bleeds	30 days	4.5%
Mose et al (29), 2006; 1991–2003	Denmark	PUB; discharge diagnosis of PUB requiring hospitalization	RCS (county hospital discharge registry)	7204	Not reported	30 days	10.7%
Murata et al (33), 2011; 2008	Japan	PUB; ICD10 coding	RCS (National administrative database; diagnosis procedure combination)	4863	Not reported	30 days	1.1% teaching hospitals, 1.6% nonteaching hospitals
Nahon et al (25), 2008; 2005–2006	France	Peptic ulcer disease/ esophagitis (excluding cases relating to portal hypertension)	PCS (53 French hospitals)	1706	New admissions only	Hospital discharge	6.5% <75 yrs (69/1069) 7.3% ≥75 yrs (46/639)
Shaheen et al (22), 2009; 1993–2005	USA	PUB; ICD9CM codes to identify primary diagnosis of PUB, or secondary diagnosis PUB if primary diagnosis was UGIB	RCS (Nationwide inpatient sample)	237,412	'Primary diagnosis of peptic ulcer bleeding'	In hospital	3.0% (weekday), 3.4% (weekend)
Soncini et al (31), 2007; 2001–2005	Italy	NVUGIH; using ICD9CM discharge coding	RCS (12 Italian hospitals)	2832	Not reported	30 days	2.6%
Sung et al (12), 2010; 1993–2005	Hong Kong	PUB; confirmed endoscopically	PCS (single-centre [Prince of Wales Hospital*])	9375	New admission and inpatient bleeds	30 days	6.2%
Thomsen et al (30), 2006; 1991–2003	Denmark	PUB; using ICD8 codes	RCS (Danish civil registry)	7232	Not reported	30 days	11%

**Sha Tin, New Territories, Hong Kong. AVH Acute variceal hemorrhage; GI Gastrointestinal; ICD* International Classification of Diseases*; NVUGIH Nonvariceal upper gastrointestinal hemorrhage; PCS Prospective cohort study; PUB Peptic ulcer bleeding; RCS Retrospective cohort study; UGIB Upper gastrointestinal bleeding; UGIH Upper gastrointestinal hemorrhage; UK United Kingdom; yrs Years of age*

coincided with the introduction of [the] ICD-10 classification system….". Careful attention to selection of well-validated coding is key to enable accurate interpretation of outcome data from such administrative databases. Use of specific registries for NVUGIB, although labour and cost intensive, enable rigorous selection of cases, usually by medical and nursing personnel, ideally prospective follow-up, adjustment for key disease-specific prognostic variables and auditing of case ascertainment (12,17,26), although they can be limited by size and inadequate population coverage.

Admission status and duration of reported patient follow-up: Careful review of selection criteria, patient sampling and length of follow-up also demonstrates subtle but important differences that may influence reported outcomes. For example, exploratory data have suggested differing health care delivery patterns between outpatient bleeds and cases in whom hemorrhage started while already hospitalized for an unrelated condition (38). Therefore, inclusion of inpatient bleeds will influence reported mortality rates considering their markedly poorer prognosis (38), with some series reporting up to a fourfold increase in mortality for inpatients developing bleeding compared with new admissions (39). One of the three Italian studies included both new admissions and existing inpatients who developed upper gastrointestinal tract bleeding (17), whereas it was unclear in the other two studies whether inpatient bleeds were included in addition to new admissions (28,31). Three studies from the United States were included, with the study by Cooper et al (40) reporting almost double the mortality rate compared with the other two studies (14,22). There were subtle differences in all three studies: all used administrative data-sets and ICD-9-CM coding to identify cases; Cooper et al (40) used Medicare claims data whereas the other two studies used data from the Nationwide Inpatient Sample (NIS) (9,21). The study by Cooper reported 30-day mortality, in contrast to inhospital mortality reported by the other two studies. Unfortunately, without direct and uniform statistical adjustment for confounders among studies, one can only speculate whether such disparities can account for the twofold differences in reported mortality within countries.

Patient-related factors: Age and presence of comorbid illnesses are highly influential prognostic factors following presentation with NVUGIB, and critical components of risk assessment scores. Age is a component of the Rockall score (41), and the presence of comorbid illnesses are key components of both the Rockall and Blatchford scores (42), both extensively validated prognostic scores following NVUGIB in a variety of global patient populations and clinically meaningful to the practicing clinician. Although we are not advocating a particular score, although one should be used routinely in clinical practice, there is increasing evidence that the Blatchford score is more useful than the Rockall score in predicting the need for endoscopic therapy, transfusion and identifying patients at low risk for discharge, but not superior to the complete Rockall score in predicting mortality (43,44). For valid comparisons of mortality rates, risk adjustment according to such factors is essential because these important prognosticators of outcome are unevenly distributed across providers and variation in baseline status could make a major contribution to observed differences in mortality rates. Risk adjustment is a complex construct that can involve patient's sociodemographic factors (eg, age, sex and race), acute clinical stability, severity of primary disease, functional status and burden of comorbidity (45). As highlighted in Table 2, there was remarkable similarity in the central measures of age in the reviewed studies, ranging from 64 to 74 years. However, there was wide variation in the characterization of comorbid illnesses, with specific NVUGIB registries more likely to detail individual comorbid illnesses, whereas administrative data sets were more likely to present composite scores such as the Charslon index (46) – a measure that is less clinically meaningful to the practicing clinician and not well validated as a component of risk-adjustment scores for NVUGIB. The Charlson comorbidity index was originally designed as a measure of the risk of one-year mortality attributable to comorbidity in a longitudinal study of generalized hospitalized patients, subsequently adapted so that ICD-9 codes could be used to calculate the index with existing administrative data. The presenting international normalized ratio (INR) has also been suggested as a useful predictor of mortality and may be a more objectively measurable proxy of comorbidity (47). A more widespread use of validated prognostic scales (and their subsequent reporting in observational studies) has been recommended (48,49) but remains very low (<2% in a recent national study [50]). It is, therefore, disappointing – but not surprising – that only two studies presented the Rockall score (16,31) and none presented the Blatchford score. Given this wide variation in characterization of comorbidities, it is difficult to make meaningful adjustments of baseline risk, hampering any ability to compare mortality rates among these studies or risk-adjust the reported information accordingly.

Ethnicity and genetic factors may also play a role. Two studies involved Asian populations while the remainder assessed western populations (Table 1). Differences among these ethnic groups may affect outcomes based on varying rates of proton pump inhibitor metabolism, *H pylori* prevalence, gastric parietal cell mass and disease acuteness, which may further limit direct comparisons of mortality (49).

Disease-related factors: Adequate risk adjustment to facilitate comparison of mortality also requires disease-specific risk adjustment. For NVUGIB, this would include the ability to adjust for features of hemodynamic shock, presenting hemoglobin/biochemical parameters, endoscopic diagnosis and stigmata of bleeding, including stigmata, that would be predictive of rebleeding. Only four of 18 studies presented all of these features, with 10 of 18 presenting none; administrative data sets were less likely to present this information. The inability to characterize disease acuity is a major limitation of many of the studies we reviewed, which further limits any direct comparison of outcomes among studies.

Health care system-related factors: It is, of course, probable that there are important differences in standards and procedures of care for NVUGIB that may account for some of the differences reported in mortality rates. These include the extent of access to emergency and resuscitative care, to timely endoscopy and available operator skills in hemostatic procedures and, in some cases, availability of surgery or radiological procedures, all of which may influence case fatality. Recent data from the United Kingdom (UK) has highlighted deficiencies in the provision of timely endoscopy for NVUGIB, with only 50% of hospitals having formal provision of a 24 h endoscopy service and 42% of high-risk patients (Rockall score ≥5) waiting more than 24 h for their index endoscopy (16). This is in contrast to other national registries in which at least 70% of endoscopies were performed within 24 h of admission (1,15,17,51). The actual national nature and representativeness of contributing sites may explain at least some of this variation.

The timeframe for performance of endoscopy may also play a role. Although there is some randomized evidence suggesting that timely endoscopy reduces transfusion requirements and duration of hospital stay (52), only more recent observational data have suggested an associated decrease in the need for surgery (24), although its impact on mortality remains uncertain and is an area for further research. The large, recently published UK audit barely failed to show an improvement in mortality associated with the availability of an after-hours endoscopy service (16). Several recent publications have also demonstrated increased mortality for patients admitted with NVUGIB on the weekend compared with a weekday (14,22,27), as has been reported for other acute medical conditions (53-55), which may have implications for processes and models of care in those countries, although other countries (France, Hong Kong, UK) have not reported such associations for NVUGIB (56-58).

Were studies reported well?

Clear reporting is necessary to enable an accurate assessment of the strengths/weaknesses in study design, conduct and analysis. The quality of reporting of randomized controlled trials has improved several years after the endorsement of the Consolidated Standards of Reporting

TABLE 2
Assessment of patient characteristics and disease severity

Author (reference), year	Age of analyzed patients, years (mean ± SD or median [IQR])	Comorbidities characterized, n	Describes				
			Baseline patient characteristics, n	Presenting hemodynamic parameters	% presenting with hematemesis	Presenting hemotological/ biochemical parameters	% with high-risk endoscopic stigmata
Ahsberg et al (18), 2011	Presented as age groups	None	0	No	No	No	No
Ananthakrishnan et al (14), 2009	Not reported (presented as age groups)	Charlson comorbidity index (Deyo modification)	5	No	No	No	No
Barkun et al (26), 2004	66±17 70 (55–79)	Mean number of comorbidities; ASA score	12	Yes	Yes	Yes	Yes
Button et al (32), 2011	64.1 (95% CI 63.9–64.4)	6	3	No	No	No	No
Chiu et al (23), 2009	41.8% >70 years of age	14 state number with >1 comorbidity	13	Yes	Yes	Yes	Yes
Cooper et al (40), 2009	78.2±0.8	Comorbidity index	9	No	No	No	No
Dorn et al (27), 2009	64.1±20.0 (weekend, n=23,339) 64.7±19.7 (weekday, n=75,636)	Elixhauser list of comorbidities	5	No	No	No	No
Hearnshaw et al (16), 2010	68 (49–81)	8 as well as presenting Rockall score	6	Yes	No	No	Yes
Kohn et al (28), 2009	68.0 (16.8)	9	5	No	No	No	No
Lanas et al (9), 2009	74.3±13.7 (fatal cases, upper/lower GI events combined); 64.8±18.4 (nonfatal cases)	Details mean number of comorbidities	7	No	No	Yes	No
Marmo et al (17), 2008	68±16 70 (53–81)	Mean number of comorbidities; ASA score	8	Yes	Yes	Yes	Yes
Mose et al (29), 2006	71 (62–82)	Charlson index	7	No	No	No	No
Murata et al (33), 2011	64.7±17.8 64.2±18.1	Charlson comorbidity index	7	No	No	No	No
Nahon et al (25), 2008	<75–54.1±14.1 (n=1076) ≥75–83.5±5.6 (n=639)	Details mean number of comorbidities	8	Yes	No	Yes	Yes
Shaheen et al (22), 2009	68 (54–78)	Elixhauser list of comorbidities	5	No	No	No	No
Soncini et al (31), 2006	67.7±16.7	Rockall score	4	No	Yes	No	Yes
Sung et al (12), 2010	61.0±18.4 (survivors [n=866]); 72.5±13.1 (nonsurvivors [n=577])	Number of severe comorbid illnesses	10	Yes	Yes	No	Yes
Thomsen et al (30), 2006	74 (62–82)	Charlson comorbidity index	6	No	No	No	No

ASA American Society of Anesthesiologists; GI Gastrointestinal; IQR Interquartile range

Trials (CONSORT) statement (59,60) by researchers and journals. However, in observational research, important information is often missing or unclear (21), which has prompted the development of the STROBE consensus statements with the aim of helping authors and journals improve methods and quality of reporting of observational studies (21). In the present review, there were notable omissions when assessing quality of reporting (Table 3). The proportion of in- versus outpatient onset of bleeding was unclear in 10 of 18 studies, and only one report provided a justification of sample size. Overall, 15 of 18 studies provided no information on missing data and how these were handled. Only four studies commented on processes for source data verification, while eight made no comments about the external validity of the reported data. Given the relatively large number of studies examining outcomes for NVUGIB, the development of a framework, similar to that recently developed to aid design and conduct of randomized controlled trials in NVUGIB (61), would help standardize reporting and enable more accurate comparisons of international data.

FUTURE DIRECTIONS

Improving reporting

Mortality following NVUGIB from most data sources remains substantial and is influenced by a multitude of patient-, disease- and health care system-related factors (Table 4). The present systematic review of available data on NVUGIB mortality suggests that investigators should strive to provide detailed descriptions of prognostic patient factors, process of care and methodological information to better inform any attempts at national comparisons of outcomes in NVUGIB. More uniform and standardized reporting is needed to facilitate baseline risk adjustment. In this respect, it would be helpful for studies to present, where possible, validated and clinically meaningful risk scores such as the Rockall (41) or Glasgow Blatchford scale (62), which incorporate both background comorbidities and acute disease acuity. For administrative data, validation of composite indexes, such as Charlson (46) and Elixhauser (63) in the setting of NVUGIB, would be helpful. As a minimum, the criteria presented in Table 3 would aid clarity and quality of reporting.

TABLE 3
Quality of reporting assessment (n=18)

	Studies, n
Description of eligibility criteria	18
Description of source of participants	18
Explains derivation of sample size	1
Description of statistical methods	18
Description of methods to examine subgroups/interactions	16
Description of methods of handling missing data	3
Discussion of data quality checks/source data verification	4
Discussion of limitations of study	17
Discussion of external validity of results	8
Discussion of source/role of funder	14

TABLE 4
Possible factors influencing mortality (case fatality rate) following nonvariceal upper gastrointestinal bleeding

Patient related	Age, sex
	Diagnostic mix (ie, percentage with malignancy, percentage with liver disease)
	Population comorbidity (ie, percentage of smokers, percentage with cardiovascular disease)
	Prevalence of pro- and antibleeding drug use (eg, acetylsalicylic acid use, proton pump inhibitor use, warfarin)
Health service related	Resuscitation facilities
	Use of blood
	Availability of endoscopy with therapeutic intervention
	Time to endoscopy (although no clear evidence yet that this is a true prognostic factor)
	Use of surgery (ie, a high surgical rate could increase mortality)
	Speed of access to secondary care
Technical	Case ascertainment/population based
	Restricted to acute gastrointestinal bleeding only (chronic bleeding defined and excluded)
	Acute admissions clearly separated from inpatient bleeding
	Adequate sample size

Improving outcomes

Reducing mortality further will be challenging in the face of an aging population and may depend on improved adherence to existing international recommendations (48) (which are currently poorly adhered to [64]), perhaps coupled to the emergence of important data on optimal resuscitation with blood components (65,66), and promising novel diagnostic (67,68) and therapeutic technologies (69).

CONCLUSIONS

The present review demonstrated wide differences in reported mortality rates from NVUGIB. We suggest that these differences are largely attributable to differences in adopted methodologies and populations studied. More uniform standards in reporting are needed; only then can true observed variations allow a better understanding of causes of death and pave the way to improved patient outcomes.

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