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SYSTEMATIC REVIEWS

The global epidemiology of upper and lower gastrointestinal bleeding in general population: A systematic review

Şiir Su Saydam, Megan Molnar, Pareen Vora

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Abstract

BACKGROUND

Gastrointestinal bleeding (GIB) is a common and potentially life-threatening clinical event. To date, the literature on the long-term global epidemiology of GIB has not been systematically reviewed.

AIM

To systematically review the published literature on the worldwide epidemiology of upper and lower GIB.

METHODS

EMBASE® and MEDLINE were queried from 01 January 1965 to September 17, 2019 to identify population-based studies reporting incidence, mortality, or case-fatality rates of upper GIB (UGIB) or lower GIB (LGIB) in the general adult population, worldwide. Relevant outcome data were extracted and summarized (including data on rebleeding following initial occurrence of GIB when available). All included studies were assessed for risk of bias based upon reporting guidelines.

RESULTS

Of 4203 retrieved database hits, 41 studies were included, comprising a total of around 4.1 million patients with GIB worldwide from 1980–2012. Thirty-three studies reported rates for UGIB, four for LGIB, and four presented data on both. Incidence rates ranged from 15.0 to 172.0/100000 person-years for UGIB, and from 20.5 to 87.0/100000 person-years for LGIB. Thirteen studies reported on temporal trends, generally showing an overall decline in UGIB incidence over time, although a slight increase between 2003 and 2005 followed by a decline was shown in 5/13 studies. GIB-related mortality data were available from six studies for UGIB, with rates ranging from 0.9 to 9.8/100000 person-years, and from three studies for LGIB, with rates ranging from 0.8 to 3.5/100000 person-years. Case-fatality rate ranged from 0.7% to 4.8% for UGIB and 0.5% to 8.0% for LGIB. Rates of rebleeding ranged from 7.3% to 32.5% for UGIB and from 6.7% to 13.5% for LGIB. Two main areas of potential bias were the differences in the operational GIB

definition used and inadequate information on how missing data were handled.

CONCLUSION
Wide variation was seen in estimates of GIB epidemiology, likely due to high heterogeneity between studies however, UGIB showed a decreasing trend over the years. Epidemiological data were more widely available for UGIB than for LGIB.

Key Words: Gastrointestinal bleeding; Gastrointestinal haemorrhage; Epidemiology; Incidence; Mortality; Case-fatality

Core Tip: This review addresses an important literature gap in summarizing the long-term global epidemiology of GIB. Epidemiological data were more widely available for UGIB than for LGIB, which were limited. Estimates of GIB were highly heterogeneous, often due to differences in case definitions, but showed a decreasing trend for UGIB incidence.

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INTRODUCTION

Gastrointestinal bleeding (GIB) is a potentially life-threatening clinical event resulting in more than 400000 hospital admissions in the United States (US) each year, and associated with substantial economic burden for healthcare systems[1,2]. Upper GIB (UGIB) is observed between the mouth and the duodenum, while lower GIB (LGIB) occurs distal to the ligament of Treitz[3,4]. Risk factors for GIB are well-established and include older age, being male, smoking, alcohol use, and medication use[5-13]. Previous reviews on the epidemiology of UGIB have focused on specific etiologies such as peptic ulcer bleeding (PUB)[11,14,15], outcomes associated with risk factors[16-18], or prediction scores[19-21], while reviews on LGIB are lacking. An overarching review of the long-term worldwide epidemiology of GIB would enable the totality of evidence on this topic to be obtained, covering decades that have seen advances in preventative measures and management. This would also help identify areas where data gaps remain, guiding future investigations. We therefore performed a systematic review of the literature with the aim of describing the long-term worldwide epidemiology of UGIB and LGIB in the general population.

MATERIALS AND METHODS

Data sources and search

EMBASE® and MEDLINE databases were queried from 01 January 1965 to September 17, 2019, using searches for the keywords 'epidemiology', 'incidence', 'prevalence', 'mortality', 'case fatality' combined with 'gastrointestinal', 'hemorrhage', 'haemorrhage', 'bleeding' in title or abstract. The search was restricted to studies in humans and those written in English. Deduplication across databases was performed by the embedded function within EMBASE® platform. The complete electronic search strategy is shown in Supplementary Table 1.

Inclusion and exclusion criteria

Following Cochrane Collaboration guidelines[3,4], we included population-based studies reporting either incidence, mortality or case-fatality rates for UGIB and/or LGIB in the general adult population. We included studies on either acute or chronic GIB, and those on variceal or non-variceal UGIB (NVUGIB). We excluded randomized controlled trials and interventional studies because they are not designed to assess epidemiology of a disease and are based on selected groups of individuals. Conference abstracts, editorials, letters, notes, and short surveys were excluded. Studies among patient subgroups (*e.g.*, cirrhotic patients, drug users), and those that investigated only specific GIB etiologies (*e.g.*, PUB, Mallory-Weiss) or degrees of bleeding (*e.g.*, massive LGIB) were also excluded, as were those where GIB was undefined, unspecified as UGIB/LGIB, or where mortality rates were not specified as

being GIB-related. When two or more publications presented data from the same or overlapping population, we included only the study conducted over the most recent period, unless the older data provided more extensive information on study endpoints.

Article screening and data extraction

Titles and abstracts were screened independently by two authors (ŞSS and MM), with disagreements resolved by cross-checks and discussions with the third author (PV). For remaining articles, full-text was reviewed. Details about the study design, population and results were extracted from each article. When rates were not reported explicitly, they were calculated from the available data (including from graphical displays) wherever possible.

Data analysis

Data were presented for UGIB and LGIB separately. Outcome measures were incidence rate, mortality rate and case-fatality rate. Incidence rates were extracted or calculated and presented as the number of patients with GIB divided by person-time, and mortality rates were extracted or calculated as the number of GIB-related deaths divided by person-time; both were expressed *per* 100000 person-years. For estimate calculations, person-time was defined as the population size of the catchment area multiplied by follow-up time (usually approximated as the study duration). Case-fatality rates were extracted or calculated as the percentage of GIB-related deaths among the total number of patients with GIB in the study population. Where available, data on rebleeding were extracted or determined as the percentage of GIB recurrences among patients with GIB. Rates were displayed using forest plots with 95% confidence intervals. Studies that reported incidence rates at different timepoints were displayed graphically to visualize temporal trends. Analyses were conducted using R on RStudio (Version 1.1.423) with ggplot2 and forest plot packages.

Assessment of bias

Risk of bias was assessed at the study level based on published guidance with amendments[22] (Supplementary Table 2). Each study was also evaluated against reporting guidelines for observational studies[23] (Supplementary Table 3). Risk of bias across all studies was not assessed as rates were presented individually for each study, and pooled cumulative estimates were not calculated.

RESULTS

A total of 4793 database hits were retrieved from the search (4203 from EMBASE®, 509 from MEDLINE). Following the screening of titles and abstracts (4415 were excluded), 353 articles remained. After full-text screening, 36 articles were retained for the final review[24-59]. A further five studies were included after screening bibliographies of full-text articles and relevant reviews[60-64](see PRISMA flowchart in Supplementary Figure 1 and hierarchical reason for exclusion in Supplementary Table 4). Of the 41 included studies (covering approximately 4.2 million individuals), 33 studies provided estimates on UGIB (eight specifically on NVUGIB), four on LGIB, and the remaining four reported data on both. Characteristics of the included studies are shown in Tables 1 and 2. Twenty-six studies were from Europe, eight from North America, six from Asia-Pacific and one from the Middle East. Of 33 studies on UGIB, eight reported estimates only for NVUGIB. No population-based study was identified that reported epidemiological variables of interest for variceal UGIB. The diagnostic procedure for GIB was endoscopy in 27 studies, and unclear for the remaining studies. Data sources used were hospital records (19 studies), administrative databases (12 studies), hospital surveys (7 studies), electronic health records, a survey cohort study (one study) and claims data combined with clinical data (one study).

Incidence of UGIB

Twenty-nine studies reported incidence rates for UGIB which ranged from 15.0 *per* 100000 person-years to 172.0 *per* 100000 person-years over 1980 to 2012 (Figure 1), with high heterogeneity across and within countries. Approximately two-thirds of incidence rates (65.5%) were within the range of 50 to 120 *per* 100000 person-years. Four studies reported estimates for NVUGIB incidence ranging from 15.0 *per* 100000 person-years to 108.0 *per* 100000 person-years, also with high heterogeneity between studies[34,38,40,54]. Incidence rates among studies that included GIB only as primary diagnosis were lower than studies that did not restrict inclusion to primary diagnosis only[35,44,52,59,64], except for when the numerator was the number of hospitalizations[42,48]. A hospital-based survey from France that included out-patient diagnosed GIB reported the highest incidence estimate of 143 *per* 100000 person-years for the year 1996[32].

There were thirteen studies that described temporal trends of UGIB incidence within the defined study years. Among these, overall declines in UGIB incidence were seen over time (Figure 2), most notably in Japan, which saw a particularly rapid decline, albeit with a spike in 2003[45]. Other studies described a slight increase in UGIB incidence between 2003–2005 followed by a decline[41,42,44,52,64]. Differences between studies that reported rates from the same country were likely due to different

Table 1 Basic information for studies

Ref.	Study period	Country (region)	Data source[1]	Design	Clinical event
Schlup *et al*[24], 1984	1 September 1980 - 28 February 1982	New Zealand (Dunedin)	Clinical data (Dunedin public hospitals)	P	UGIB
Katschinski *et al*[25], 1989	1 April 1984 - 31 March 1986	UK (Nottingham)	Clinical data (The Nottingham City and University Hospitals)	P	UGIB
Longstreth[26], 1995	1991	USA (San Diego)	Administrative claims database (KPMCP)	R	AUGIB
Bramley *et al*[27], 1996	October 1991 - September 1993	Scotland (Grampian and the Northern Isles)	Clinical data (Aberdeen Royal Infirmary)	P	LGIB
Masson *et al*[28], 1996	October 1991 - September 1993	Scotland (Orkney and Shetland)	Clinical data (Aberdeen Royal Infirmary)	P	UGIB
Blatchford *et al*[60], 1997	September 1992 - Feb 1993	West Scotland	Clinical data (Multicenter)	P	AUGIB
El Bagir *et al*[29], 1997	May 1991 - May 1993	Saudi Arabia (Abha City)	Clinical data (Asir Central Hospital)	P	AUGIB
Longstreth[30], 1997	January 1990 - December 1993	USA (San Diego)	Claims (KPMCP)	R	ALGIB
Soplepmann *et al*[61], 1997	1 August 1992 - 31 July 1994	Finland (Central Finland)	Clinical data (Central Hospital of Central Finland)	P	AUGIB
		Estonia (Tartu)	Clinical data (Tartu University Hospital)		
Vreeburg *et al*[31], 1997	July 1993 - July 1994	Netherlands (Amsterdam area)	Hospital survey (Two university and ten regional hospitals)	P	AUGIB
Czernichow *et al*[32], 2000	1 January - 30 June 1996	France (Finistere, Gironde, Seine Maritime and Somme)	Hospital survey (29 public hospitals and 96 private practices)	P	AUGIB
Paspatis *et al*[33], 2000	February 1998 - February 1999	Greece (Heraklion, Crete)	Hospital survey	P	AUGIB
Tenias Burillo *et al*[34], 2001	April 1995 - March 1999	Spain (Valencia)	Clinical data (Lluis Alcanyis Hospital)	P	NVUGIB
Lewis *et al*[62], 2002	1992 - 1999	USA	Hospital survey (NHDS)	R	UGIB
van Leerdam *et al*[63], 2003	January 2000 - January 2001	Netherlands (Amsterdam area)	Hospital survey (Two university and ten regional hospitals)	P	AUGIB
Targownik *et al*[35], 2006	1993 - 2003	Canada	Administrative database (HPOID)	R	AUGIB
Theocharis *et al*[36], 2008	January 1995- December 1995	Greece (Achaia)	Clinical data (Three regional hospitals)	R	AUGIB
	January - December 2005			P	
Kapsoritakis *et al*[37], 2009	1 December 2005 - 30 November 2006	Greece (Thessaly, Larissa)	Clinical data (University Hospital of Larissa)	P	AUGIB
Lanas *et al*[38], 2009	1 January 1996 - 30 December 2005	Spain	Administrative database (10 hospitals of Spanish NHS)	R	NVUGIB LGIB
Loperfido *et al*[39], 2009	1 October 1983 - 31 December 1985	Italy (Treviso)	Clinical data (Treviso Hospital)	P	AUGIB
	1 January 2002 - 31 March 2004				
Åhsberg *et al*[40], 2010	1 January - 31 December 1984	Sweden (Skåne)	Clinical data (Lund University Hospital)	R	NVUGIB LGIB
	1 January - 31 December 1994				NVUGIB LGIB

	1 January - 31 December 2004				NVUGIB LGIB
Button *et al*[41], 2011	1 April 1999 - 31 March 2007	Wales	Linked administrative database (PEDW)	R	UGIB
Langner *et al*[42], 2011	2000 – 2005	Germany	Administrative database (GHS)	R	UGIB
Crooks *et al*[43], 2012	1 April 1997 - 30 August 2010	England	Linked EHR data (GPRD and HES)	R	UGIB
Laine *et al*[44], 2012	2001 - 2009	USA	Administrative claims database (Premier Perspective)	R	UGIB LGIB
Miyamoto *et al*[45], 2012	1997 - 2008	Japan (Aki-Ota, Hiroshima)	Clinical data	R	UGIB
Mungan *et al*[46], 2012	6 January - 10 March 2009	Turkey	Cohort study (ENERGIB survey)	R	NVUGIB
Nahon *et al*[47], 2012	March 2005 - February 2006	France	Hospital survey (53 hospitals)	P	UGIB
Sangchan *et al*[48], 2012	1 October 2009 - 30 September 2010	Thailand	Claims and clinical data	R	UGIB
Del Piano *et al*[49], 2013	June 2006 - June 2007 and December 2008 - December 2009	Italy	Clinical data (13 hospitals)	P	ANVUGIB
Hreinsson *et al*[50], 2013a	1 January 2010 - 31 December 2010	Iceland (Reykjavik)	Clinical data (National University Hospital of Iceland)	P	ALGIB
Hreinsson *et al*[51], 2013b	1 January 2009 - 31 December 2010	Iceland (Reykjavik)	Clinical data (National University Hospital of Iceland)	P	AUGIB
Cavallaro *et al*[45], 2014	January 2001 - December 2010	Italy (Veneto)	Administrative database (HDRs)	R	UGIB LGIB
Marmo *et al*[53], 2014	March 2003 - March 2004 and April 2007 - May 2008	Italy	Administrative database (PNED1 and PNED2)	P	NVUGIB
O'Byrne *et al*[54], 2014	1 January 2008 - 31 December 2009	Canada (Saskat-chewan)	Clinical data (SHR and RQHR)	R	NVUGIB
Abougergi *et al*[64], 2015	1989 - 2009	USA	Administrative database (NIS)	R	UGIB
Niikura *et al*[55], 2015	1 July 2010 - 31 March 2012	Japan	Administrative claims database (DPC)	R	LGIB
Taha *et al*[56], 2015	2007 - 2012	Scotland (Ayrshire)	Clinical data (University Hospital Crosshouse)	R	UGIB
Lu *et al*[57], 2018	1 January 2008 - 31 December 2012	China	Hospital survey (Eight hospitals)	R	NVUGIB
Park *et al*[58], 2018	February 2011 - December 2013	South Korea (Daegu, Gyeong-sang)	Clinical data (Eight hospitals)	P	UGIB
Wuerth *et al*[59], 2018	2002 - 2012	USA	Administrative database (NIS)	R	UGIB

[1]Clinical data: Hospital records; Hospital survey: Survey or standardized questionnaire being administered to multiple hospitals or healthcare practices to gather clinical records; Administrative database: Inpatient data collected by government or research organizations. Linkage refers to combining information from multiple data sources of the same population, removing duplicates.

EHR: Electronic health records; EMR: Electronic medical records; KPMCP: Kaiser Permanente Medical Care Program; HDRs: Health Discharge Records; HPOID: Health Person-Oriented Information Database; NHS: National Health Services; PEDW: Patient Episode Database for Wales; ENERGIB: European Survey of Non-Variceal Upper Gastro Intestinal Bleeding; GHS: German Hospital Statistics; GPRD: General Practice Research Database; HES: Hospital Episodes Statistics; PNED: Progetto Nazionale Emorragie Digestive; SHR: Saskatoon Health Region; RQHR: Regina Qu'Appelle Health Region; NIS: Healthcare Cost and Utilization Project Nationwide Inpatient Sample; DPC: Diagnosis Procedure Combination; P: Prospective; R: Retrospective; ALGIB: Acute lower gastrointestinal bleeding; AUGIB: Acute gastrointestinal bleeding; ANVUGIB: Acute nonvariceal upper gastrointestinal bleeding; LGIB: Lower gastrointestinal bleeding; NVUGIB: Nonvariceal upper gastrointestinal bleeding; UGIB: Upper gastrointestinal bleeding.

Table 2 Study characteristics, *n* (%)

Ref.	Diagnostic criteria	Total patients, (male)	Age[1], (mean)	Population at risk	Re-bleeding	Diagnostic endoscopy[2]	In-hospital bleeds[3]
Schlup *et al*[24], 1984	Hematemesis and/or melena	112 (58.0)	≥ 15 (61.5)	120000 - 150000	18 (16.1)	Yes	Unclear
Katschinski *et al* [25], 1989	Hematemesis and/or melena	1017 (N/A)	All (N/A[6])	789000	N/A	Yes	Unclear
Longstreth[26], 1995	ICD-9-CM	258 (63.6)	≥ 20 (60.6)	270699	N/A	Yes	Yes
Bramley *et al* [27], 1996	Suspected UGIB or LGIB	252 (46.8)	All (N/A[6])	467760	34 (13.5)	Some	Yes
Masson *et al* [28], 1996	Suspected UGIB or LGIB	1098 (62.2)	All (N/A[6])	468000	N/A	Yes	Yes
Blatchford *et al* [60], 1997	Hematemesis and/or melena; using standard definitions	1882 (64.2)	≥ 15 (N/A[6])	2184285	N/A	Some	Yes
El Bagir *et al* [29], 1997	Hematemesis and/or melena	240 (62.5)	≥ 20 (44.3)	450000	N/A	Yes	Unclear
Longstreth[30], 1997	ICD-9-CM	219 (55.7)	≥ 20 (67.2)	N/A	14 (6.7)	Yes	Yes
Soplepmann *et al*[61], 1997	Hematemesis and/or melena	270 (66.7)	≥ 15 (64.2)	257000	N/A	Yes	Yes
		243 (60.0)	≥ 15 (58.8)	159000	N/A		
Vreeburg *et al* [31], 1997	Hematemesis, melena, hematochezia, or blood admixture upon nasogastric aspiration	951 (60.0)	All (Mdn: 71)	1610900	156 (16.4)	Yes	Yes
Czernichow *et al* [32], 2000	Hematemesis and/or melena	2133 (63)	≥ 18 (Mdn: 68)	2926241	N/A	Yes	Yes
Paspatis *et al* [33], 2000	Hematemesis, melena or other clinical or laboratory evidence of blood loss from the upper GI tract	353 (63.5)	≥ 16 (66.2)	220000	41 (12)	Yes	Yes
Tenias Burillo *et al*[34], 2001	All admitted patients with UGIB	779 (62.1)	Adults (63.4)	180996	N/A	Yes	Unclear
Lewis *et al*[62], 2002	ICD-9-CM	N/A	All (N/A)	N/A	N/A	Unclear	Yes
van Leerdam *et al*[63], 2003	Hematemesis, melena, hematochezia, or blood admixture upon nasogastric aspiration	769 (56.0)	All (N/A[6])	1612439	119 (16.0)	Yes	Yes
Targownik *et al* [35], 2006	ICD-9 and ICD-10-CA	142363[4] (N/A)	≥18 (62.0-66.0)	21944828-24324251	N/A	Unclear	No
Theocharis *et al* [36], 2008	Hematemesis, bloody nasogastric aspiration, or melena and clinical/laboratory evidence of acute blood loss from the upper GI tract	489 (74.4)	> 16 (59.4)	300078	48 (9.9)	Yes	Yes
		353 (72.5)	> 16 (66.1)	326794	26 (7.3)		
Kapsoritakis *et al*[37], 2009	All patients hospitalized for acute UGIB	264 (75.4)	≥ 16 (65.5)	228428	21 (7.9)	Yes	Yes
Lanas *et al*[38], 2009	ICD-9-CM	17663[4] (N/A)	All (N/A[6])	3281973 - 3681822	N/A	Unclear	No
		5769[4] (N/A)					
Loperfido *et al* [39], 2009	ICD-9	532 (72.3)	> 15 (61.0)	231914	191 (32.5)	Yes	Yes
		513 (64.3)	> 15 (68.7)	266791	40 (7.4)		
Åhsberg *et al* [40], 2010	ICD-8	138 (75.0)	Adults (Mdn: 69)	151711	N/A	Yes	Unclear
		69 (46.0)	Adults				

			(Mdn: 69)				
	ICD-9	123 (60.0)	Adults (Mdn: 73)	170727			
		95 (45.0)	Adults (Mdn: 76)				
	ICD-10	181 (59.0)	Adults (Mdn: 77)	289560			
		125 (54.0)	Adults (Mdn: 75)				
Button *et al*[41], 2011	ICD-10	22299[5] (54.4)	≥ 18 (64.1)	N/A	N/A	Some	Yes
Langner *et al* [42], 2011	ICD-9-GM	94232[5] (51.4)	All (N/A[6])	N/A	N/A	Unclear	No
Crooks *et al*[43], 2012	ICD-10 (HES) and Read code system (GPRD)	347085	≥ 18 (N/A[6])	N/A	N/A	Unclear	Unclear
Laine *et al*[44], 2012	ICD-9	N/A	All (N/A)	N/A	N/A	Unclear	No
Miyamoto *et al* [45], 2012	Hematemesis and/or melena	2367 (53.7)	All (67.9)	Approximately 16065	N/A	Yes	Unclear
Mungan *et al* [46], 2012	ICD-9/ICD-10	423 (67.4)	Adults (57.8)	N/A	28 (6.6)	Yes	Yes
Nahon *et al*[47], 2012	Hematemesis and/or melena and/or acute anemia with blood in the stomach	3203 (66.5)	≥ 18 (Mdn: 64.1)	N/A	317 (9.9)	Yes	No
Sangchan *et al* [48], 2012	ICD-10	77111[5] (69.2)	Adults (58.5)	N/A	N/A	Some	No
Del Piano *et al* [49], 2013	Presenting to the emergency room for NVUGIB	1413 (66.0)	All (53.2)	N/A	77 (5.4)	Yes	No
Hreinsson *et al* [50], 2013a	(1) Passage of bright red blood per rectum or maroon colored without hematemesis and (2) Melena with no bleeding in upper GI endoscopy	131 (49.7)	≥ 18 (Mdn: 68)	151008	N/A	Yes	Yes
Hreinsson *et al* [51], 2013b	(1) Hematemesis or coffee ground vomit; (2) Melena; and (3) Rectal bleeding with confirmed bleeding on upper gastroendoscopy and negative colonoscopy	132 (58.0)	18-105 (Mdn: 71)	N/A	N/A	Yes	Yes
Cavallaro *et al* [45], 2014	ICD-9-CM	23450 (59.5)	All (64.2)	4912438	N/A	Unclear	No
		13800 (47.8)					
Marmo *et al* [53], 2014	Hematemesis, melena or dark, tarry materials on rectal examination	2317 (65.9)	≥ 18 (67.9)	N/A	86 (3.7)	Yes	Yes
O'Byrne *et al* [54], 2014	ICD-10	360 (61.7)	17-100 (66.5)	1200000	73 (20.3)	Yes	Yes
Abougergi *et al* [64], 2015	ICD-9-CM	1266426[4] (54.5)	All (Mdn: 67.0-70.0)	N/A	N/A	Yes	No
Niikura *et al* [55], 2015	ICD-10	30846 (52.0)	≥ 20 (Mdn: 74)	N/A	N/A	Unclear	No
Taha *et al*[56], 2015	ICD-10	869[4] (62.5)	All (Mdn: 63)	258370 -260280	N/A	Unclear	Unclear
Lu *et al*[57], 2018	(1) Hematemesis and/or melena; (2) Drainage of coffee grounds or fresh blood in the gastric tube; (3) Positive FOBT; and (4) Varices, but endoscopy confirmed that bleeding was unrelated	2977 (76.5)	≥ 18 (54.7)	N/A	87 (2.9)	Yes	Yes
Park *et al*[58], 2018	Hematemesis, melena, and hematochezia or a suspicious clinical presentation of UGIB such as syncope, epigastric pain, dyspnea, dizziness, altered mental status, or anemia	1424 (74.1)	≥ 16 (62.7)	N/A	110 (7.7)	Yes	No

Wuerth *et al* [59], 2018	ICD-9-CM	2432088 (55.0)	≥ 18 (N/A[6])	N/A	N/A	Some	No

[1]Age category of patients included in the study, given in years. If not defined in the methods, the age range of included participants is stated. Median age is noted, when mean age is not available. Mdn: median.
[2]Endoscopy, colonoscopy, sigmoidoscopy or any other diagnostic screening methods being used to identify or validate the diagnosis of patients as a standard procedure.
[3]Including bleeding events that occurred while the patient is being hospitalized for another disease. In administrative databases, if patients only have a primary diagnosis of GIB, in-hospital bleeds are assumed to not be included.
[4]Total number of patients across the entire study period is provided. Stratified data for each year is available in full text.
[5]The value reflects the number of hospitalizations, not the number of patients.
[6]Distribution of the number of patients is available for each age group.
ICD: International Classification of Diseases (ICD-8: ICD, Eight Revision; ICD-9: ICD, Ninth Revision; ICD-10: ICD, Tenth Revision; ICD-9-CM: ICD-9, Clinical Modification; ICD-9-CA: ICD-9, Canadian Adaptation; ICD-9-GM: ICD-9, German Modification); FOBT: Fecal occult blood test; GI: Gastrointestinal; ANVUGIB: Acute nonvariceal upper gastrointestinal bleeding; LGIB: Lower gastrointestinal bleeding; NVUGIB: Nonvariceal upper gastrointestinal bleeding; UGIB: Upper gastrointestinal bleeding.

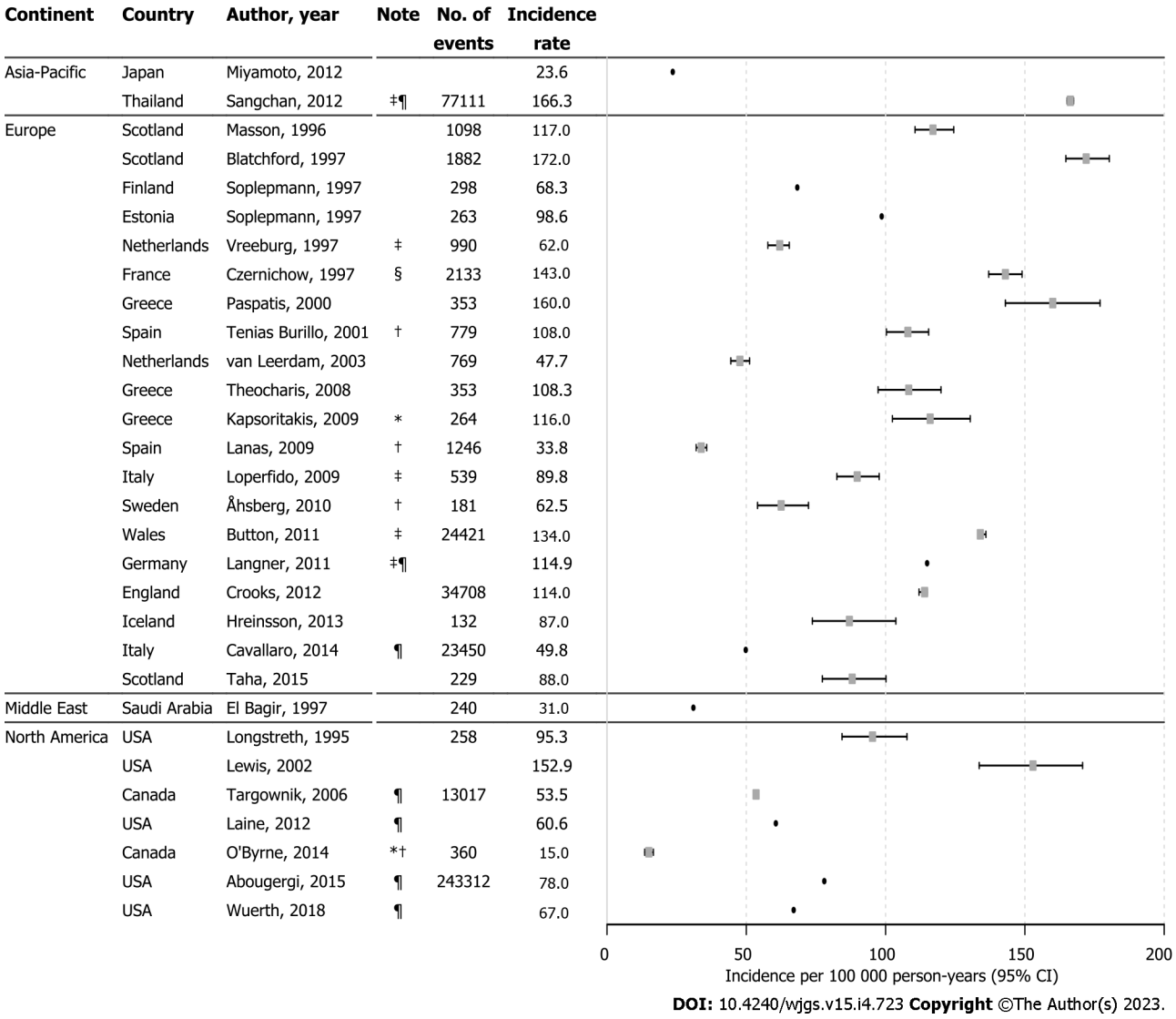

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Figure 1 Forest plot of upper gastrointestinal bleeding incidence rates. This figure displays incidence rates of upper gastrointestinal bleeding *per* 100000 person-years with 95% confidence intervals (when reported) from studies included in the review that reported this information. *Calculated from the available data (not originally presented in the paper). †NVUGIB. ‡Calculated from hospitalizations (not the number of patients). §Included out-patient bleeds. ¶Included UGIB cases only if primary diagnosis. Estimates were marked as a point without 95%CI, when denominator was missing. CI: Confidence interval; NVUGIB: Non-variceal upper gastrointestinal bleeding; UGIB: Upper gastrointestinal bleeding; USA: United States of America.

inclusion criteria and GIB definition. Among two studies from Italy in 2004, one reported a rate of 84.8 *per* 100000 person-years for UGIB incidence with the inclusion of hospital bleeds based on clinical data [39], while the other reported a rate of 52.4 *per* 100000 person-years for emergency GIB-related admissions from administrative data with a larger sample size[52]. In the US, estimates for UGIB incidence from three administrative database studies, which identified GIB using primary diagnosis codes, ranged from 60 to 110 *per* 100000 person-years across several timeframes between 1989 and 2012 [44,59,64]. Also from the US, a hospital-based study reported higher UGIB incidence at 152.9 *per* 100000 person-years over their 1992–1999 study period, where GIB cases were not limited to primary diagnosis only[62].

UGIB-related mortality

Mortality was reported in six studies; UGIB-related mortality was not reported directly in four and so estimates were calculated from available data[28,37,54,61]. Estimates ranged from 0.88 to 9.75 *per* 100000 person-years (Figure 3). Two studies with large sample sizes reported mortality rates for NVUGIB as 1.1 *per* 100000 person-years using clinical data from Spain[38] and 1.83 *per* 100000 person-years in Canada based on administrative claims[54]; these were lower than most mortality estimates of overall UGIB.

UGIB case-fatality

Case-fatality rates for UGIB were reported in 15 studies with estimates ranging from 0.7% to 4.7% (Figure 4**)**. Case-fatality for NVUGIB ranged between 1.6% and 4.0%, with higher rates from studies that restricted to UGIB as the primary diagnosis[25,35,49]. In four studies, the number of UGIB-related deaths was very low, leading to imprecise estimates[24,26,37,46]. UGIB case-fatality rates varied across regions during 1980–2013, although higher rates were reported in earlier years, particularly in Europe.

Incidence of LGIB

Six studies reported incidence rates for LGIB; estimates ranged between 20.5 and 87.0 *per* 100000 person-years[27,30,40,44,50,52], with the lowest estimate from a US claims database in study years from 1990-1993[30] and the highest from a single hospital-based study from Iceland in 2010[50]. In Scotland, the incidence of LGIB was found to be 27 *per* 100000 person-years based on a study using hospital records for the period 1990–1993[27], while for the same period, a claims-based study from the US reported a rate of 20.5 *per* 100000 person-years[30]. Another US claims database study reported a LGIB incidence rate of 41.8 *per* 100000 person-years for the year 2001[44]. Analysis of administrative data from the Veneto region in Italy (with a population around 5 million), reported an incidence of LGIB in 2001 of 27.3 *per* 100000 person-years[52]. Studies reporting time trends in LGIB incidence found that rates fluctuated across time, with higher rates observed during 2001–2005[44,52]. In a hospital study from Sweden, rates decreased from 55.6 to 43.2 *per* 100000 person-years over a 10-year period starting from 1994[40].

LGIB-related mortality

Three studies reported estimates for LGIB-related mortality[27,38,40]. Using data from 10 hospitals within the Spanish National Health System and covering a population of around 4 million, Lanas *et al* [38] demonstrated that LGIB-related mortality increased from 0.2 to 1.0 *per* 100000 person-years between 1996 and 2005. A single-center hospital based study from Grampian and the Northern Isles in Scotland found LGIB-related mortality to be 1.4 *per* 100000 person-years over a 10-year study period (1994–2004) [27], while over the same time period, an increase in LGIB-related mortality was observed in Sweden from 0.59 to 3.45 *per* 100000 person-years[40].

LGIB case-fatality

Six studies reported LGIB case-fatality rates with estimates ranging from 0.5% to 8.0%[27,30,38,40,50,55]. LGIB case-fatality among patients in Spain fluctuated over 1996–2005, increasing from 2.9% in 1996, peaking at 5.0% in 1999, and declining to 2.6% in 2005[38]. Based on 170727 hospital records in Sweden between January-December 1994, LGIB case-fatality increased from 1.0% to 8.0% over a 10-year study period (1994–2004) albeit based on only 69 LGIB cases[40]. Other reported LGIB case-fatality rates range from 0.5% in a US claims database study on 219 cases between 1990 and 1993[30] to 5.1% from a hospital-based study in Scotland with 252 cases over an overlapping period (1991–1993)[27]. More contemporary LGIB case-fatality rates from Japan and Iceland were reported as 2.5%[55] and 1.2%[50], respectively.

Rebleeding (UGIB/LGIB)

Seven studies reported UGIB rebleeding rates. These ranged from 7.3% to 32.5% with rebleeding rates being generally lower in the more contemporary studies. Five studies reported NVUGIB rebleeding rates ranging from 2.9% to 20.3%. Rebleeding rates for LGIB were reported in two studies covering the 1990s; the rates were 13.5%[27] and 6.7%[30].

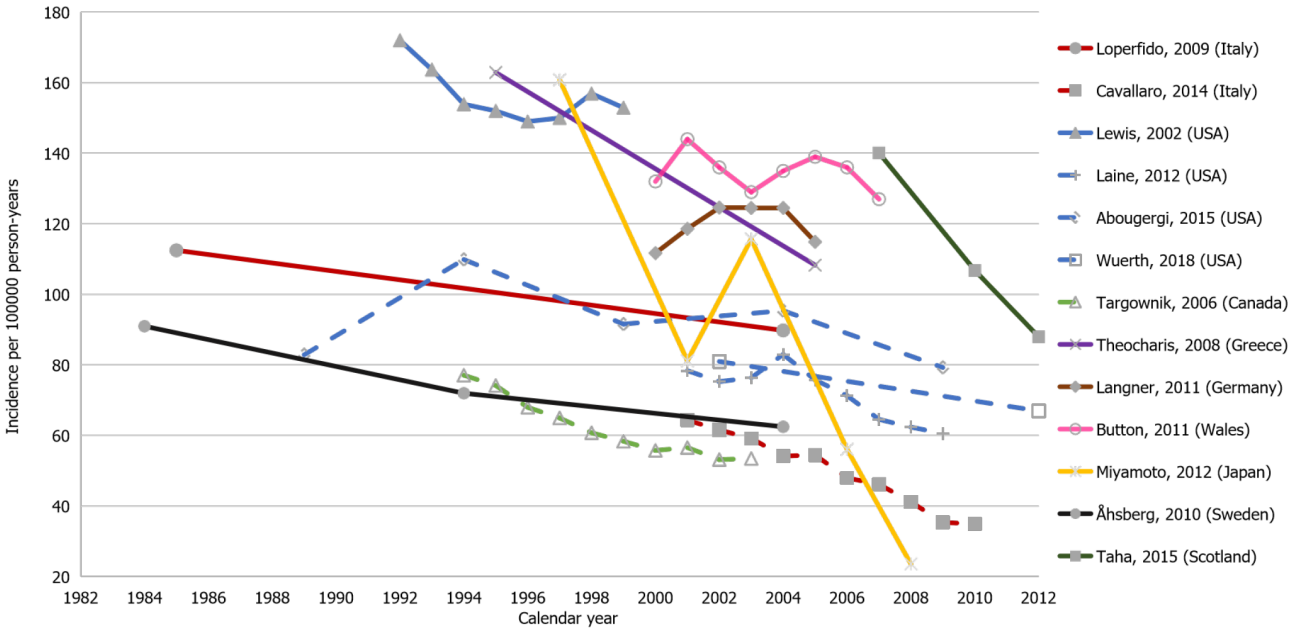

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Figure 2 Temporal trends of upper gastrointestinal bleeding incidence. This figure displays data from studies that reported on incidence rates of upper gastrointestinal bleeding *per* 100000 person-years over time from studies included in the review that reported this information. Note: Studies that include UGIB data only as primary diagnosis are indicated with dashed lines. UGIB: Upper gastrointestinal bleeding. USA: United States of America.

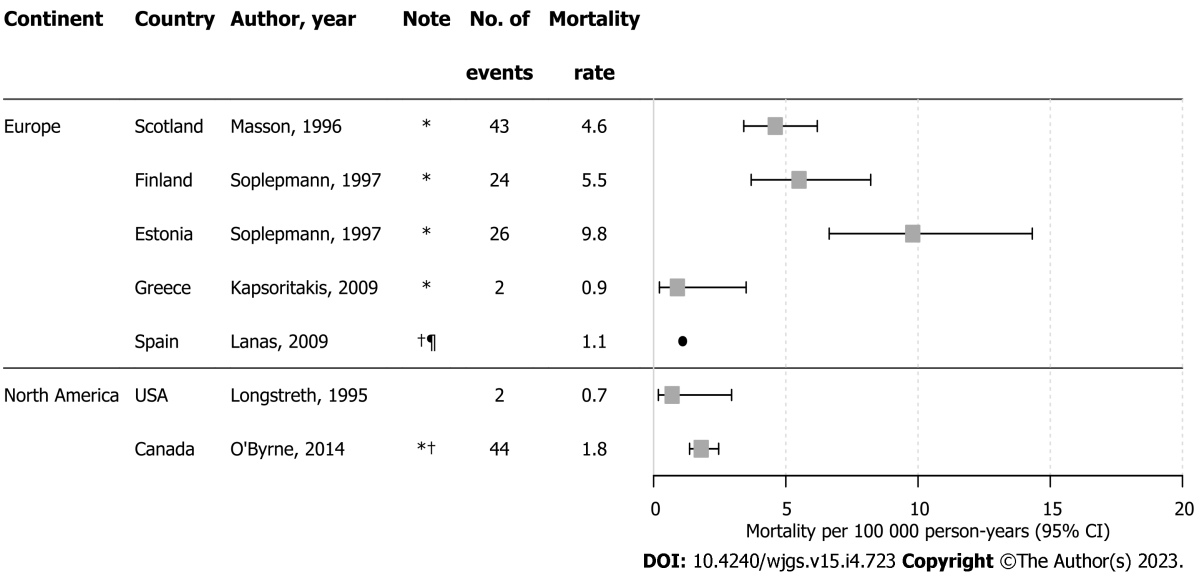

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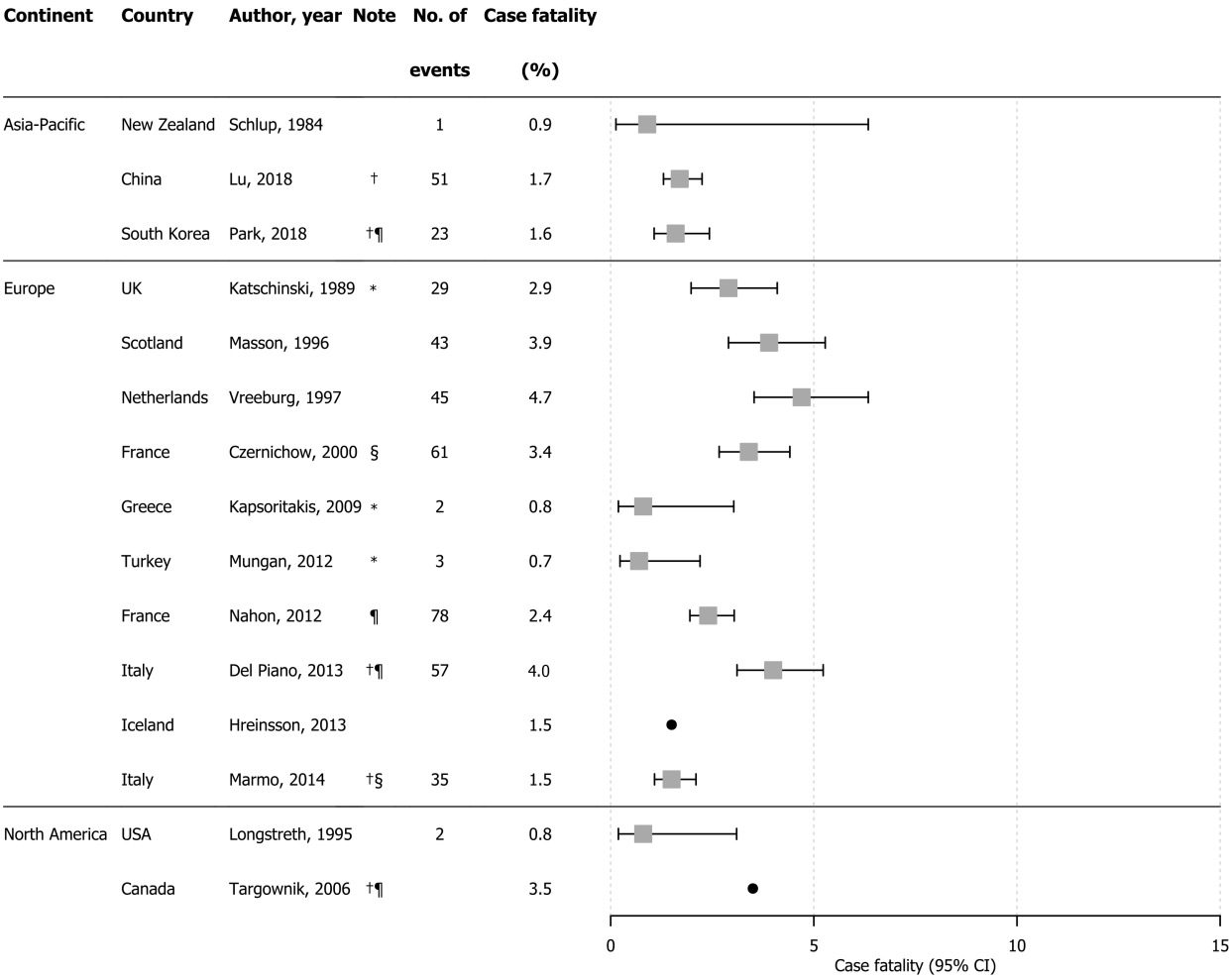
Figure 3 Forest plot of upper gastrointestinal bleeding mortality rates. This figure displays upper gastrointestinal bleeding mortality rates *per* 100000 person-years with 95% confidence intervals (when reported) from studies included in the review that reported this information. Estimates were marked as a point without 95%CI, when denominator was missing. *Calculated from the available data (not originally presented in the paper). †NVUGIB. ‡Calculated from hospitalizations (not the number of patients). §Included out-patient bleeds. ¶Included UGIB cases only if primary diagnosis. CI: Confidence interval; NVUGIB: Non-variceal upper gastrointestinal bleeding; UGIB: Upper gastrointestinal bleeding; USA: United States of America.

Risk of bias and methodological reporting guideline assessment

Two main potential areas of bias were identified: UGIB/LGIB definition and inadequate information on how missing data were handled (Supplementary Figure 2, Supplementary Table 5). Based on the assessment of individual studies, 2 out of 19 studies that used standardized classification methods failed to provide UGIB/LGIB codes, despite adopting ICD criteria for classification[55,56]. Only 12 out of 41 studies described how they handled missing data – by excluding individuals with missing data in their records. The low risk of bias domains were the identification of target population and the appropriate sampling of patients. Thirty-nine percent of studies reported adequate information on the inclusion of patients in the study, and 42% presented thorough descriptive data on patient characteristics



DOI: 10.4240/wjgs.v15.i4.723

Figure 4 Forest plot of upper gastrointestinal bleeding case-fatality rates. This figure displays case-fatality rates of upper gastrointestinal bleeding, with 95% confidence intervals (when reported) from studies included in the review that reported this information. Estimates were marked as a point without 95%CI, when denominator was missing. *Calculated from the available data (not originally presented in the paper). †NVUGIB. ‡Calculated from hospitalizations (not the number of patients). §Included out-patient bleeds. ¶Included UGIB cases only if primary diagnosis. CI: Confidence interval; NVUGIB: Non-variceal upper gastrointestinal bleeding; UGIB: Upper gastrointestinal bleeding; USA: United States of America.

(Supplementary Table 6). Only 29% of studies described the generalizability of their results.

DISCUSSION

Gastrointestinal bleeding is an important clinical event associated with high patient burden and major resource implications for healthcare systems. Our review provides broad insights into the long-term worldwide epidemiology of GIB in the general adult population. Incidence, mortality, and case-fatality rates for GIB were found to vary substantially across and within countries. For UGIB, estimates ranged from 15.0 *per* 100000 to 172.0 *per* 100000 person-years for incidence (with a decline seen over time), 0.9 per 100000 to 9.8 *per* 100000 person-years for UGIB-related mortality, 0.7% to 4.8% for case-fatality, and 7.3%–32.5% for rebleeding. For LGIB, estimates ranged from 20.5 *per* 100000 person-years to 87.0 *per* 100000 person-years for incidence, 0.2 *per* 100000 person-years to 1.0 *per* 100000 person-years for LGIB-related mortality, 0.5% to 8.0% for case-fatality, and 6.7%–13.5% for rebleeding.

Our results are in line with findings from earlier reports of a decreasing trend of UGIB incidence[15], albeit the data were heterogeneous likely due to methodological differences such as inclusion criteria and the operational definition of GIB. These differences resulted mainly from either restriction to hospital cases or the inclusion of patients where GIB was the sole primary diagnosis. For example, a high UGIB incidence of 143 *per* 100000 person-years was observed in France, where 16% of the 2133 included UGIB cases were managed out of the hospital setting[32], compared with a much lower rate of 49.0 *per* 100000 person-years reported in Italy where patients with GIB as the sole primary diagnosis were included[63]. Incidence rates from studies that restricted UGIB cases to those resulting in a hospital admission may have been underestimated. This is noteworthy because over time, UGIB cases

deemed at low risk have tended to be treated on an outpatient basis[35]. Similarly, in terms of deaths, exclusion of deaths before hospital arrival would likely result in mortality underestimation, although the assumption that severe GIB cases would be admitted to inpatient settings could lead to overestimations of case-fatality. The clinical definition of GIB differed across studies, and those that used clinical markers for UGIB (such as anemia) reported higher incidence rates[32,58]. In other studies where cases with another primary diagnosis were excluded, incidence rates were generally lower, and possibly underestimated. In addition, among administrative database studies, differences in inclusion criteria were observed in the standardized codes *(e.g.*, ICD-10) used to ascertain GIB. Diagnostic differences in GIB have been reported by others[3], and in our risk of bias assessment, a high proportion of studies demonstrated a high risk of classification bias for GIB cases. Aside from differences in methodologies, heterogeneity in GIB epidemiology over our decades long inclusion period could be attributed to changes in both the prevalence of risk factors and clinical practice over time. Changes in social deprivation[27,30,60,65], administration of acid suppressive therapy with proton-pump inhibitors[31,49,63,65], as well as risk inducing medication use such as selective serotonin reuptake inhibitors and non-steroidal anti-inflammatory drugs have all been associated with GIB prevalence in the literature[11,39,40,66,67]; a detailed review of these was beyond the scope of this review. Incomplete information on patient characteristics was a domain of high risk, which makes it difficult to assess differences in clinical markers across studies.

The limited data on LGIB were unsurprising because, relative to UGIB, it is less commonly encountered in clinical practice, and research would understandably be more focused on the latter. Diagnosis is also more challenging for LGIB as illustrated in one study where 25% of undefined cases of hematochezia, originally suspected to be sourced from the lower GI tract, were later confirmed as UGIB [40]. Additionally, most therapeutic advancements did not benefit bleeding sites beyond the duodenum [68,69] and surgical interventions were less effective for LGIB compared to UGIB due to difficulties in bleeding localization[52]. This could limit the exploration on the epidemiology LGIB, as less impact would be expected on the management of the event upon lacking advancements and studies presenting data on LGIB would remain limited. Our review also revealed limited published data on UGIB-related mortality and case-fatality. Where reported, UGIB-related mortality was low, possibly indicative that of UGIB death is more commonly a result of advanced comorbidities rather than an excessive bleed *per se*. Previous studies have shown that while peptic ulcer is the most frequent cause of UGIB in hospital settings, death in UGIB cases more commonly occur due to gastric cancer or esophageal varices[25,26,31,61]. With further research on UGIB-related death, clinical management strategies could be devised more effectively to target the predictors of UGIB incidence, independently from those for mortality.

This review has several strengths. We systematically reviewed the literature on the long-term worldwide epidemiology of GIB across geographies, and we are unaware of any previous study to have done this. Systematic reporting of disease epidemiology across geographical regions – where patients may differ in their characteristics and where differences in clinical management through diagnosis and treatment may occur – is important for identifying factors that could influence estimates of occurrence. We identified areas of differences in study methodology and reporting, applying risk of bias assessment, to explicate variability across studies. In terms of limitations, we only included studies written in English, although this has not been associated with systematic bias in other reviews[70,71]. Some articles published before 1991 may not have been captured as database indexing was suboptimal at this time with low sensitivity of keyword search[72]; however, bibliography of relevant articles and reviews were scanned to minimize information bias. Additionally, all studies on variceal bleeding identified during the search were either small and not population-based, and/or had no epidemiological variables of interest reported, therefore we were unable to describe the epidemiology of variceal bleeding. Lastly, estimates were not pooled due to the limited number of included studies and their study heterogeneity, which could limit the applicability of findings to inform about the real-world epidemiology of GIB.

CONCLUSION

Our systematic literature review describes wide ranging estimates of the long-term epidemiology of GIB, which is likely due to high heterogeneity between studies. Overall, the incidence of UGIB showed a decreasing trend over the years. Epidemiological data were more widely available for UGIB than for LGIB.

ARTICLE HIGHLIGHTS

Research background

Gastrointestinal bleeding (GIB) can be a life-threatening medical event; however, reviews on the overall global epidemiology of the condition are lacking. Previous reviews have instead covered risk factors or

prediction scores for GIB or have described the epidemiology of GIB arising from specific etiologies.

Research motivation

No overarching review on the broad and long-term worldwide epidemiology of GIB currently exists. A systematic review would be highly informative for future research in the field to provide a robust overview of GIB incidence, mortality and case-fatality.

Research objectives

The objective was to perform a systematic review of the long-term global epidemiology of both upper GIB (UGIB) and lower GIB (LGIB), covering incidence, mortality and case-fatality of the condition. Such population-based estimates would enable trends over time, and by geography, to be observed, which could have been influenced by changing medical practices, and it would also help identify areas where data are plentiful or lacking.

Research methods

A search strategy using relevant keywords was conducted using EMBASE® and MEDLINE from 1 January 1965 to 17 September 2019. Conference abstracts, editorials, letters, notes, and short surveys were excluded, as well as randomized controlled trials and interventional studies (as these are performed among selected individuals, and do not enable population-based epidemiological estimates to be calculated). Two authors undertook the screening of titles, abstracts and full-texts of papers. Data on the epidemiological variables of interest were extracted.

Research results

Thirty-six studies were included. The main findings were that the incidence of UGIB ranged from 15.0 to 172.0/100000 person-years and the incidence of LGIB ranged from 20.5 to 87.0/100000 person-years, although data for LGIB were more limited than for UGIB. Temporal trends were described in 13 studies and showed an overall decline in upper GIB incidence over time. UGIB mortality rates ranged from 0.9 to 9.8/100000 person-years, and from 0.8 to 3.5/100000 person-years for LGIB; case-fatality rate ranged from 0.7 to 4.8% for UGIB and 0.5 to 8.0% for LGIB.

Research conclusions

Substantial variation exists in estimates of GIB epidemiology worldwide, likely due to high heterogeneity between studies, highlighting a lack of consistency in GIB definitions. As data on LGIB epidemiology were sparse, this area should be further explored in future research.

Research perspectives

The proposed direction of future research would be to obtain contemporary estimates of UGIB and, especially LGIB epidemiology from large, high quality, population-based studies with good case ascertainment and case validation.

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FOOTNOTES

Author contributions: Saydam SS and Vora P designed the research study; Saydam SS, Molnar M and Vora P performed the research; Saydam SS analyzed the data and wrote the manuscript; All authors have read and approved the final manuscript.

Conflict-of-interest statement: Saydam SS and Vora P are employees of Bayer AG. Molnar M was an employee of Bayer AG at the time the study was carried out.

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