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REVIEW ARTICLE

Endoscopic retrograde cholangiopancreatography (ERCP): lessons learned from population-based national registries: a systematic review

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Abstract

Background Endoscopic retrograde cholangiopancreatography (ERCP) was introduced more than four decades ago as a diagnostic tool for biliary and pancreatic diseases. Currently, ERCP is mainly used as a therapeutic approach to relieve biliary or pancreatic duct obstruction. Clinical practice has been based on a few large reports and some randomized controlled trials. These data are valuable and important, but the external validity of these reports is limited. Implementation into routine practice should be balanced with the knowledge that these studies were conducted under very specific circumstances. This review was undertaken to describe ERCP results from population-based national registries recorded during routine clinical practice.

Methods A systematic literature search of the electronic databases Medline Ovid and Embase was conducted. Eligible papers were selected and data were recorded according to the PRISMA criteria.

Results Thirty-one studies were included: 15 true national population-based and 16 population-level studies. Most studies originated from countries with a governmental public health care system. At least three-quarters of the ERCP procedures are currently therapeutic, and the technical success rate is high (> 90%). The postprocedure 30-day mortality rate ranged between 1 and 5% and was strongly correlated with older age, male sex, emergency admission, and noncancer comorbidities, but exhibited a lower correlation with the annual ERCP volume. Patients with primary sclerosing cholangitis or liver cirrhosis should receive particular attention. The risk of developing a bile duct, liver, or pancreas malignancy after ERCP tended to increase, but endoscopic sphincterotomy did not affect this risk.

Conclusion ERCP is currently mainly used as a therapeutic approach, and the results are generally likely to improve patients' conditions. A nationwide registry enables better monitoring of routine clinical practice. The collection of valuable information from routine clinical practice in population-based databases may help to improve patient care from best evidence to best practice.

Keywords ERCP · National · Registry · Population-based · Outcomes

Since the introduction of endoscopic retrograde cholangiopancreatography (ERCP) in 1968 [1], the technique has rapidly become established in clinical practice as a valuable diagnostic tool for the evaluation of biliary and pancreatic

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diseases. The therapeutic potential of this endoscopic approach was discovered when endoscopic sphincterotomy was described in Germany [2] and Japan [3]. ERCP, which is currently mainly employed as a therapeutic approach, is regarded a routine procedure worldwide [4–8]. However, concerns have emerged regarding the definition and identification [9] of procedure-related complications (i.e., post-ERCP pancreatitis, bleeding, perforation, and others) and how these complications are recognized and recorded [5, 10–12]. Recently, both the quality and development of ERCP [13] and gastrointestinal endoscopy in general [14], as well as the methodological quality of guidelines in gastroenterology, have been addressed [15]. Clinical experience and knowledge are mainly obtained from various reports published by experts who are often affiliated with high-volume academic centers. However, a number of concerns, including variations in the patient case mix, referral patterns, and treatment traditions between institutions, may introduce bias, which may hamper the interpretation and restrict the generalizability of results. Randomized controlled trials (RCTs) may circumvent many of these obstacles. The well-defined inclusion and exclusion criteria of RCTs may, however, limit the external validity and hamper the extrapolation of the results and recommendations for an unselected population [16]. Thus, a number of challenges arise when introducing best evidence and clinical guidelines into routine clinical practice [17].

This review was undertaken to describe the outcomes of ERCP examinations reported in population-based national registries based on the recordings obtained in routine clinical practice. Furthermore, the goal was also to evaluate the impact of these observations in relation to current clinical ERCP practice.

Materials and methods

A systematic literature search was conducted. The electronic databases Medline Ovid (1965–2018) and Embase (1974–2018) were searched for relevant publications using a strict search strategy; combinations of the following medical subject headings (MeSH) and key words were used: endoscopic retrograde cholangiopancreatography, ERCP, registry, registries, register, population-based, national, and regional. In addition, a manual search of relevant full-text articles was performed. Search strings are provided electronically in Supplementary Box 1.

Single-institution series, multicenter studies, RCTs, systematic reviews and meta-analyses, surveys, nonpublished conference reports or abstracts, and studies without information on population-based patient inclusion or registries were excluded. In addition, we excluded papers that addressed topics beyond the scope of the ERCP procedure, which were regarded as irrelevant for the topic being study.

Eligible papers were selected and data were recorded according to the PRISMA criteria [18, 19] and are outlined in Fig. 1.

This study was an evaluation of eligible scientific literature already published, and an IRB approval or any written consent did not apply to this scientific work according to legislations in Norway and Sweden.

Results

Thirty-one full-text articles were identified (Fig. 1), including 15 true national population-based studies [20–34] (Table 1) on various aspects of the ERCP procedure. In addition, another 16 studies (Table 2) with a population-based-level design were considered relevant [6, 7, 10, 12, 35–46]. These 16 studies were based on data recorded from a particular region in a country or a well-defined geographical area, with a referral population representing the general population of the catchment area, or likely mirroring an unselected general population of that country.

Origins of the studies

The majority (12/15) of the studies (Table 1) were performed in Sweden. The remaining three studies were performed in Denmark [25] and England [20], and as a collaboration between Sweden and Finland [29], respectively. While the governmental Swedish Hospital Discharge Register and the Swedish Cancer Registry were used in six of the 14 population-based studies [23, 28–31, 33] (Table 1), six papers [21, 22, 24, 26, 27, 32] were based on data reported to the Swedish Registry for Gallstone Surgery and ERCP ('GallRiks'), and finally two papers were based on data from the NHS database in the UK [20] and the Danish National Patient Registry [25], respectively. The reports listed in Table 1 are regarded as true population-based studies because the sources are national governmental administrative databases or prospective national clinical databases with mandatory prospective reporting according to national legislation (e.g., the 'GallRiks' ERCP database in Sweden).

The 16 reports listed in Table 2 are by definition not true national population-based cohort studies. However, these reports are regarded as population-level-based studies because they contain data from a region or another well-defined area of a country with a catchment population that is similar to the general population. Four of these studies [41, 43, 45, 46] were performed in the USA based on the Nationwide Inpatient Sample (NIS) database. The NIS is a part of the Healthcare Cost and Utilization Project (HCUP). This database comprises approximately

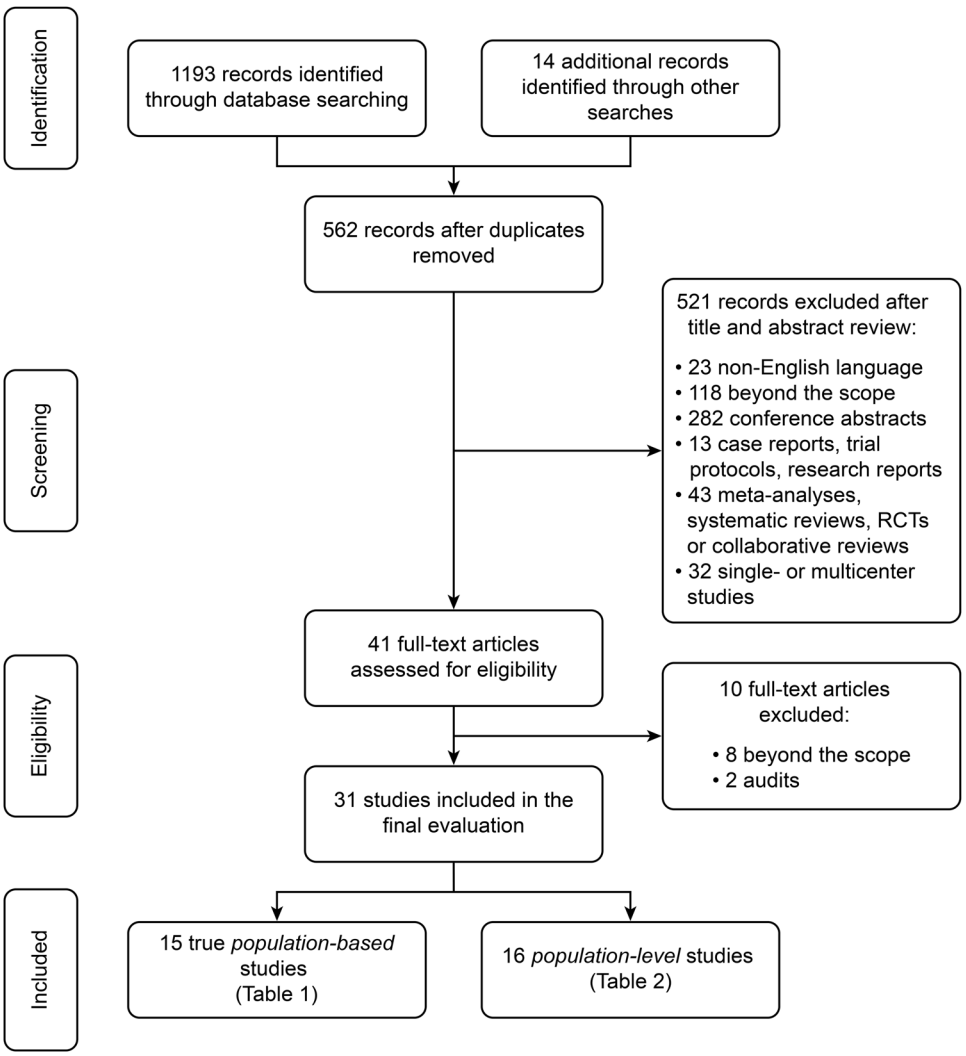

Fig. 1 Identification of eligible studies from the literature databases

8 million hospital stays from approximately 1000 hospitals in 45 states and is designed to approximate a 20% stratified sample of patients from all hospitals in the United States, as explained recently in more detail by other researchers [42]. In addition, another report from the USA takes advantage of the same HCUP organization but employs the Kids' Inpatient Database (KID) to evaluate trends in the utilization of ERCPs in children at the population level [44]. Observations of several thousands of patients from the Alberta region [39] and the province of Manitoba [40] in Canada have been reported. The benchmarking project from Austria [7], the community practice project from Minnesota [10], the 'GastroNet' projects from Norway [6, 12, 37, 38], and the 1-year study from the Netherlands [36] increase the diversity of approaches. While their limitations as nonnational cohorts are recognized, we still believe that these studies are highly relevant population-level studies and thus of particular interest for this review (Table 2).

Information provided by population-based registries

A wide variety of issues have been addressed in population-based registries, including the general use and availability of ERCP in the community, technical success rates, therapeutic procedures, complications or adverse effects, and other factors [21, 22, 25, 27, 29, 31].

Use and indications for ERCP

According to the 'GallRiks' registry in Sweden, which includes 2 years (2007–2008) of data from consecutive patients, the registry comprised 97.3% of all ERCP cases. Two-thirds (66%) of the ERCPs had an emergency/urgent indication, and 13% of procedures were performed on an outpatient basis [21]. In the Alberta region, the use of ERCP was stable over several years, with an average ERCP rate of 0.85 per 1000 for men and 1.12 per 1000 for women

Table 1 Studies based on national population-based ERCP registries

Authors	Journal year	Country-setting	No. of patients/procedures	Time period	Topic under evaluation	Authors' conclusion
Karlson et al. [23]	Br J Surg 1997	Sweden; Swedish Cancer Registry	992 patients All ES performed in Sweden during the study period	1977–1985	Risk of cancer incidence in organs adjacent to the sphincter	With a follow-up of 9–10 years after an ES for CBDS, the risk of cancer in the pancreas, liver, and bile ducts was not affected, nor was the long-term survival
Strömberg et al. [30]	Clin Gastroenterol Hepatol 2008	Sweden; Sweden Hospital Discharge Register and Swedish Cancer Registry	27,708 patients underwent an ERCP, among which 11,617 underwent an ES	1976–2003	Risk of biliary malignancy after ERCP/ES	Increased risk of malignancy in the bile ducts, liver, or pancreas after ERCP in patients with benign disease; ES does not affect the risk
Mortensen et al. [25]	J Natl Cancer Inst 2008	Denmark; National Patient Registry and the Danish Cancer Registry	10,690 patients who underwent ERCT and 10,690 patients who underwent ERCP with sphincterotomy	1977–2003	Risk of cholangiocarcinoma after ES	ES was not causally related to an increased risk of developing cholangiocarcinoma
Enochsson et al. [21]	Gastrointest Endosc 2010	Sweden: Swedish Registry for Gallstone Surgery and ERCP (GallRiks)	11,074 ERCP procedures	2007–2008	Cannulation rates and peri- and postoperative complication rates	ERCP is widely used at Swedish hospitals, with a biliary cannulation success rate of 92%. Peri- and postoperative complications rates were 2.5% and 9.8%, and the 30-day mortality rate was 5.9%, which is similar to established standards
Strömberg et al. [31]	Br J Surg 2011	Sweden: Swedish Hospital Discharge Registry and Swedish Cancer Registry	126,885 procedures in 110,119 patients	1965–2009	Evaluation of treatment approaches for CBDS and identification of factors influencing mortality	90-day mortality rates after open surgery, ERCP, and laparoscopic treatment were 0.2, 0.8, and 0%, respectively. After adjusting for confounding factors, no difference in mortality after open surgery and ERCP was found
Bodger et al. [20]	Gastrointest Endosc 2011	England: HES data from the NHS trusts	20,246 first ERCP procedures and 20,22 first ERCP procedures	2006–2007 2007–2008	Evaluation of all-cause mortality after the first ERCP based on administrative data from English hospitals with linkage to the death register	The 30-day mortality rate was 5.3%. Predictors of mortality included older age, male sex, emergency admission, and noncancer comorbidity. However, no correlation with ERCP volume was identified

Table 1 (continued)

Authors	Journal year	Country-setting	No. of patients/procedures	Time period	Topic under evaluation	Authors' conclusion
Strömberg et al. [28]	Surg Endosc 2012	Sweden, Stockholm County Region; Sweden Hospital Discharge Register and Swedish Cancer Registry	323 cases vs. 200 controls; 90 patients vs. 146 controls were eligible	1990–2003	Post-ERCP mortality and risk factors for 90-day mortality after ERCP for nonmalignant disease	The 90-day mortality rate was 1.6%. Advanced age, severe comorbidities, high complexity of the procedure and the occurrence of a complication were associated with mortality
Swahn et al. [32]	Am J Gastroenterol 2013	Sweden: Swedish Registry for Gallstone Surgery and ERCP (GallRiks)	Case–control study with 452 patients with PEP compared to 12,718 ERCP procedures	2007–2009	Whether rendezvous bile duct cannulation during ERCP reduces the risk of PEP	The rendezvous cannulation technique reduced the risk of PEP from 3.2 to 2.6% compared with conventional biliary cannulation ($p=0.02$). However, the number-needed-to-treat (NNT) was as high as 71
Enochsson et al. [22]	JAMA Surg 2013	Sweden: Swedish Registry for Gallstone Surgery and ERCP (GallRiks)	Observational study of 63,685 cholecystectomies and 37,860 ERCPs	2005–2011	To describe the establishment of a nationwide validated web-based quality registry of gallstone surgery and ERCP	GallRiks is a validated national quality registry for gallstone surgery and ERCP, serving as a basis for the audit of gallstone disease treatment. It also provides a database for clinical research
Olson et al. [26]	Scand J Gastroenterol 2015	Sweden: Swedish Registry for Gallstone Surgery and ERCP (GallRiks)	47,950 ERCPs, but 31,188 examinations were analyzed	2005–2013	Potential advantages of the use of prophylactic antibiotics in patients undergoing ERCP	The risk of adverse events was reduced by 26% following the prophylactic use of antibiotics. However, the absolute risk reduction of 2.6% was modest
Lubbe et al. [24]	Endoscopy 2015	Sweden: Swedish Registry for Gallstone Surgery and ERCP (GallRiks)	36,358 ERCPs, including 408 cholangioscopy procedures	2007–2012	To address the use and outcomes of cholangioscopy in wider clinical practice	Postprocedural adverse events were more prevalent when cholangioscopy was used (19.1% vs. 14.0%). Pancreatitis (7.4% vs. 3.9%) and cholangitis (4.4% vs. 2.7%) were ERCP-specific adverse events that were elevated in the cholangioscopy group

Table 1 (continued)

Authors	Journal year	Country-setting	No. of patients/procedures	Time period	Topic under evaluation	Authors' conclusion
von Seth et al. [34]	Liver International 2015	Sweden: Swedish Registry for Gallstone Surgery and ERCP (GallRiks)	8932 adults who underwent ERCP, including 141 patients with primary sclerosing cholangitis (PSC)	2007–2009	To study adverse events following ERCP and to evaluate if PSC is a risk factor for pancreatitis	PSC was an independent risk factor for pancreatitis, OR 2.02, cholangitis, OR 2.88, and extravasation of contrast, OR 5.84. Careful selection of patients with PSC who are eligible for ERCP, as well as a need for high competence of the treatment team, is recommended
Kalaitzakis et al. [33]	Dig Dis Sci 2015	Sweden: Swedish Discharge Registry and Swedish Death Registry	12,675 first ERCPs for benign disease at 66 hospitals	2005–2008	To investigate predictors of ERCP outcomes, primarily early re-admission and all-cause mortality, but also, secondarily, technical failure	The lower hospital ERCP volume was related to failed ERCP procedures and was associated with a longer LOS. Failed ERCP and lower hospital procedure volume were associated with poor survival
Strömberg et al. [29]	Endosc Int Open 2016	Population-based cohort study of all patients registered for an ERCP in the governmental inpatient registries in Finland and Sweden	69,925 ERCP procedures, including 40,193 in which ES was performed, were eligible for evaluation	1976–2008	To study the risk of malignancy after ERCP in the bile ducts in a larger cohort d with a longer follow-up	An elevated risk of malignancy both in the bile ducts alone and in the bile ducts, liver, and pancreas together was observed after ERCP. The risk was the same regardless of whether ES had been performed; therefore, ES was unlikely to be the cause
Olsson et al. [27]	UEGJ 2017	Sweden: Swedish Registry for Gallstone Surgery and ERCP (GallRiks)	43,595 ERCP procedures	2006–2014	To evaluate the use of prophylactic pancreatic stenting (PS) in a nationwide register-based study in which the primary outcome was the prophylactic effect of PS on reducing PEP	PS with a diameter > 5 Fr and length > 5 cm exerted a better protective effect on PEP than shorter and thinner stents

Table 2 Studies based on regional or other population-level-based ERCP registries

Authors	Journal year	Country-setting	No. of patients/procedures	Time period	Topic under evaluation	Authors' conclusion
Hilsden et al. [39]	Can J Gastroenterol 2004	Canada: Alberta region, population-based administrative database	21,005 ERCPs in 15,036 patients	1994–2002	Pattern of use of ERCP in a Canadian province	ERCP use remained relatively stable over a period of 8 years, but the proportion of therapeutic procedures increased dramatically
Kapral et al. [7]	Endoscopy 2008	Austria; "Benchmarking ERCP" Project, including 28 of 150 ERCP sites	3132 ERCP procedures	2006	Quality assessment program for high-risk endoscopic procedures	Success and complication rates were compared to those reported elsewhere. Endoscopists with an annual case volume > 50 ERCPs had higher success rates and lower overall complication rates
Colton et al. [10]	Gastrointest Endosc 2008	Eight community hospitals in the Minneapolis-St. Paul area, Minnesota, USA	805 ERCPs in 696 patients	December 1 2005–July 31, 2006	To determine ERCP quality outcomes, including complications, in a community practice	In this community practice, complication rates compared very favorably with those of academic centers. The technical success rates achieved the rates recommended by the ASGE/American College of Gastroenterology Task Force
Glomsaker et al. [37]	Scand J Gastroenterol 2011	Norway: National survey for four different years, including all hospitals with ERCP services	42,260 procedures; (annual average ≈ 3842 ERCPs)	1999, 2002, 2005, and 2009	Temporal trends in ERCP in a national context	During this 10-year period, the number of hospitals with an ERCP service and the number of procedures decreased. The proportion of ERCP procedures performed by gastrointestinal surgeons decreased

Table 2 (continued)

Authors	Journal year	Country-setting	No. of patients/procedures	Time period	Topic under evaluation	Authors' conclusion
Glomsaker et al. [6]	Scand J Gastroenterol 2011*	Norway: prospective population-level multicenter study	3809 ERCP procedures	2007–2009	Pattern of use of ERCP in a national context	The main indications were bile duct treatment (86.2%) and sphincterotomy (46.2%); treatment for CBDS (37.6%) and the insertion of a CBD stent were the most common therapeutic procedure. Chronic pancreatitis was rare, and sphincter Oddi disease (SOS) was never reported as an indication
Glomsaker et al. [38]	Scand J Gastroenterol 2013	Norway: prospective population-level multicenter study	2808 ERCP procedures (i.e., 94.6% of all available procedures for the study population)	2007–2009	To evaluate the self-reported pain experienced by patients and satisfaction related to the ERCP procedure	One-third of the patients who underwent ERCP experienced moderate to severe pain during the procedure, and an association between pain experience and overall satisfaction with the treatment was observed. However, a paradox was observed, as most patients generally reported that they were satisfied despite undergoing a painful procedure
Glomsaker et al. [12]	Br J Surg 2013	Norway: prospective population-level multicenter study	2808 ERCP procedures (i.e., 94.6% of all available procedures for the study population)	2007–2009	Incidence and pattern of complications after ERCP and identification of risk factors for complications	ERCP is a procedure with a considerable risk of complications. Morbidity (11.6%) and procedure-related mortality (1.4%) are related to patient age and comorbidities, but also to the hospital ERCP volume and type of therapeutic intervention

Table 2 (continued)

Authors	Journal year	Country-setting	No. of patients/procedures	Time period	Topic under evaluation	Authors' conclusion
Moffat et al. [40]	Gastrointest Endosc 2014	Canada: Manitoba Health, a regional general health care provider for every individual in the province of Manitoba	31,607 ERCPs in 21,556 individuals	1984–2009	To establish population-based rates of ERCP, evaluate changing indications, and evaluate interactions between the cholecystectomy technique and ERCP use	ERCP use increased steadily during the study period and shifted from a diagnostic to a therapeutic modality
James et al. [46]	Clin Gastroenterol Hepatol 2014	USA: NIS, the largest inpatient database in the USA, consisting of a 20%, stratified, random sample of all nonfederal inpatient admissions	166,438	1998–2008	To evaluate a suggested decrease in in-hospital mortality from acute pancreaticobiliary conditions, and to further investigate the impact of patient-related factors on in-hospital mortality, length of stay, and hospital costs	Over time, a reduced in-hospital mortality rate (1.1–0.6%) caused by cholangitis, choledocholithisasis, and acute pancreatitis in patients who underwent ERCP was shown. Diagnostic ERCP use decreased from 28.8 to 10.0%. While the proportion of hospitals performing < 100 ERCPs per year decreased, no differences were observed in mortality, LOS, or hospital costs based on hospital ERCP volumes
Pant et al. [44]	J Pediatr Gastroenterol Nutr 2014	USA: KID, Healthcare Cost and Utilization Project (HCUP), which are based on data from nonfederal community hospitals. The database comprises a stratified random sample of individual hospitalizations of patients aged ≤ 20 years at the time of admission	22,153 ERCPs	Four annual cohorts: 2000, 2003, 2006, and 2009	To investigate the recent trends in the volume of ERCPs performed in children within the United States	Children who underwent ERCP were more likely to be older, female, and Hispanic compared with hospitalized children who did not undergo this procedure. An increasing use of therapeutic ERCP was observed

Table 2 (continued)

Authors	Journal year	Country-setting	No. of patients/procedures	Time period	Topic under evaluation	Authors' conclusion
Ekkelenkamp et al. [36]	Endoscopy 2015	The Netherlands (≈50% of all ERCPs nationally)	8575 ERCPs at 61 centers	One-year report in 2014	To assess procedural outcomes of ERCP within a large prospective registry in The Netherlands, and to evaluate associations between endoscopist-related factors and procedural outcomes	"Degree of difficulty," "intact papillary anatomy," and "previous ERCP failure" were independently associated with procedural failure. "Yearly volume of ERCPs" and "trainee involvement" were independently associated with success
Clark et al. [45]	Endosc Int Open 2016	USA: NIS	61,322 octogenarians who underwent an ERCP	2007–2010	To characterize the mortality and length of stay of octogenarians undergoing inpatient ERCP	ERCP is routinely performed during inpatient admission for octogenarians with biliary tract diseases. The mortality of octogenarians is higher than in previous reports, likely due to an infection occurring during the same admission
Cooper et al. [35]	Surg Endosc 2017	USA: NIS	110,811 ERCPs in the NIS database	2007–2009	To evaluate whether differences in training background for surgeons and gastroenterologists correlate with differences in outcomes for ERCP, and to evaluate specialty-related practice pattern variables that may impact those outcomes	Gastroenterologists and surgeons have different outcome profiles with respect to ERCP outcomes that warrant further investigation and discussion, and may partially be related to differences in practice patterns Lower volume providers achieve inferior outcomes, regardless of specialty background

Table 2 (continued)

Authors	Journal year	Country-setting	No. of patients/procedures	Time period	Topic under evaluation	Authors' conclusion
Navaneethan et al. [43]	Endosc Int Open 2017	USA: NIS database	All patients with cirrhosis who underwent ERCP (3228) matched (1:4) with 12,912 noncirrhotic patients who underwent ERCP	2010	To assess the prevalence of various ERCP-related averse events in patients with cirrhosis, to compare the rates of adverse events with noncirrhotic controls, and to evaluate the impact of cirrhosis on adverse events, length of stay, and hospital costs	ERCP was performed safely in patients with cirrhosis, with the caveat that it may increase the risk of postprocedural bleeding. Performing biliary sphincterotomy judiciously and the referral of patients with cirrhosis to large hospitals for ERCPs may improve outcomes
Parikh et al. [41]	Surg Endosc 2018	USA: NIS database	77,323 patients with cholangitis due to choledocholithiasis who underwent an ERCP	1998–2012	To assess the trends in ERCP utilization in patients with cholangitis due to choledocholithiasis. Length of stay, in-hospital mortality, and inflation-adjusted costs were analyzed for three groups characterized by urgent	The prevalence of acute cholangitis due to choledocholithisas doubled during the study period (15 years), accompanied by an increase in overall ERCP rates, and for urgent ERCP < 24 h in particular. ERCP within 24–48 h resulted in a significant reduction in LOS and in-hospital mortality. Inflation-adjusted hospital charges increased for all ERCP groups, most notably in the ERCP > 48 h group, which displayed a more than threefold increase

[39]. The proportion of therapeutic procedures increased over time [39, 40]. Important variations within the Alberta region were encountered [39]. Regional variations were also reported from Norway [6], but these variations plateaued during a 10-year time period between 1999 and 2009. Moreover, during the same time period, the total number of ERCP procedures and the number of hospitals with an ERCP service decreased [6]. A progressive increase in ERCP rates has also been reported in the USA [41] and notably in children [44].

The most common indication for ERCP has been the treatment of common bile duct stones (CBDS) [37].

ERCP as a therapeutic procedure

While the average ERCP rate remained stable in the Alberta region between 1994 and 2002 [39], the proportion of therapeutic ERCP procedures increased from 33 to 70% during the same period. This finding is consistent with figures reported from Sweden, where 75% of the ERCP procedures were therapeutic in the mid-2000s [21]. An even higher proportion (91.6%) of therapeutic ERCP interventions were performed between 2007 and 2009 in Norway [12].

Technical success

Successful bile duct cannulation, which is often interpreted as a technical success, was reported to at a rate of 92% by Enochsson et al. [21] and 91.6% by Glomsaker et al. [12]. Similar success rates were reported from a community practice in the USA [10]. A benchmarking project from Austria reported a general success rate of 84.8%, and success was positively correlated with the annual number of ERCPs performed by the endoscopist (> 50/year) [7]. These observations are consistent with figures from the Netherlands, with a general success rate of 85.8% [36]. Procedural failure was independently associated with the "degree of difficulty," "intact papillary anatomy," and "previous ERCP failure." Success was also independently associated with "yearly volume of ERCPs" and "trainee involvement" [36].

Complications and mortality

The Swedish national 'GallRiks' study [22] reported relatively constant intra- (2.8%) and postoperative (12.0%) complications rates between 2005 and 2011, with the exception of a slight increase from 3.6 to 5.6% in the frequency post-ERCP pancreatitis in patients who underwent elective ERCP. In another large Swedish nationwide study [31] on the treatment of CBDS, including 126,885 procedures in 110,119 patients, the authors concluded that after adjustment for confounding factors, no difference in mortality was observed between patients with CBDS who received treatment with open surgery and ERCP [31]. In a population-based case–control study by Strömberg et al. [28] on patients who underwent ERCP for a nonmalignant disease between 1990 and 2003, a 90-day mortality rate of 1.6% was reported (Table 2). Factors associated with an increased risk of death were older age, severe comorbidity, high complexity of the procedure, and the occurrence of a complication [28].

Bodger et al. [20] from the UK addressed the 30-day all-cause mortality after ERCP as a candidate indicator of care. While age, male sex, emergency admission, cancer, and non-cancer comorbidity were independent predictors of 30-day mortality, no correlation with hospital ERCP volume was identified. The mortality risk for patients requiring ERCP was regarded as comparable across English hospitals [20].

Old age has been a concern regarding treatment with ERCP. In the NIS study from the USA on octogenarians (mean age 84.2 years) who underwent ERCP between 2007 and 2010, the in-hospital mortality rate was 3.1% [45] (Table 3). The authors found that biliary stone disease

Table 3 Key findings of this literature review

- While ERCP was introduced in the early 1970s, the first report on population-based ERCP registries was published in 1997.
- The majority of the identified publications originate from the Nordic countries, a few European countries, and Canada
- With the advent of novel imaging modalities, currently ERCP is employed as a therapeutic procedure in at least three-quarters of the procedures
- Main indications include biliary tract treatment for CBDS and sphincterotomy
- The technical success rate is high (> 90%), and the procedure-related mortality is low (1–5%), and mostly related to higher age, male sex, emergency admission, and noncancer comorbidities
- The number of hospitals with a low case volume (annually < 50–100 ERCPs) has decreased, and outcomes including overall complication rates seem to be inversely associated with annual procedure volume
- An increased risk of hepato-biliary-pancreatic malignancy after ERCP is likely, but this is not causally related to whether an ES has been performed or not
- Great care should taken when considering the use of ERCP in patients with significant liver disease (e.g., liver cirrhosis, PSC) which can impact severe complications
- In patients with significant liver disease (e.g., liver cirrhosis, PSC), the indications and use of ERCP need particular considerations in regard to the balance between possible clinical benefits against the risk of severe complications of an ERCP procedure in this particular group of patients

(55.9%) was the most common discharge diagnosis, and an infection was recorded in 45% of the patients. Infection was associated with a significantly higher risk of in-hospital mortality [45].

In another NIS-based study from 1998 to 2008 comprising 166,438 admissions for acute biliary conditions, the in-hospital mortality rate decreased from 1.1 to 0.6%, and diagnostic ERCPs decreased from 38.4 to 26.9%. Moreover, the rate of unsuccessful ERCPs decreased from 6.3 to 3.2%.

ERCP is an important therapeutic tool in the management of patients with primary sclerosing cholangitis (PSC). Based on the findings from a nationwide 2-year cohort study using the Swedish population-based 'GallRiks' registry (Table 1), von Seth and coworkers [34] identified a significantly increased risk of overall adverse events after ERCP in 141 patients with PSC (18.4%) compared with patients without PSC (7.3%), with an odds ratio (OR) of 2.02 (95% confidence interval (CI) 1.04–3.92) for developing post-ERCP pancreatitis, an OR of 2.88 (95% CI 1.47–5.65) for cholangitis, and an OR of 5.84 (95% CI 2.24–15.23) for the risk of extravasation of contrast (i.e., perforation).

The safety and outcome of ERCP in patients with cirrhosis has been a concern and has not been evaluated in a larger series. In a very recent study based on information from the NIS database in the USA, a matched case–control study was designed by comparing ERCP outcomes of 3228 patients with cirrhosis with 12,912 noncirrhotic patients [43]. An increased risk of postprocedural bleeding was observed in patients with cirrhosis (both compensated and decompensated) and when therapeutic ERCP with biliary sphincterotomy was employed.

Risk of malignancy after previous ERCP/endoscopic sphincterotomy (ES)

Karlsson and coworkers reported findings for a follow-up study of all Swedish patients ($n=992$) who underwent an ES between 1977 and 1985 to evaluate possible risk aspects for malignancy in the liver, bile ducts including the ampullary region and pancreas after previous ERCP, and ES [23]. With a follow-up of 10 years and using data reported to the national cancer registry, the authors did not detect an increased risk of developing cancer in adjacent organs. The same topic was evaluated by Strömberg and coworkers [30] in a large-scale follow-up study of patients who underwent ERCP from 1976 to 2003 for benign disease (Table 2). The Swedish Hospital Discharge Register was cross-linked to the Swedish Cancer Registry. The risk of malignancy in bile ducts alone and the combination of the bile ducts, liver, and pancreas was significantly increased (standardized incidence ratio (SIR) 3.3; 95% CI 2.3–4.5) in the total cohort. However, ES did not seem to affect this risk. Undiagnosed cancers may have been present in this cohort prior to the ERCP. Recently, Strömberg et al. [29] reported findings for an even larger population-based cohort study from Sweden and Finland, with 69,925 patients undergoing ERCP between 1976 and 2008. Consistent with the results from the previous study, an increased risk of bile duct, liver, and pancreas malignancies was observed (SIR 2.3; 95% CI 2.1–2.5). However, this increased risk was not related to whether patients underwent an ES. Furthermore, Mortensen et al. [25] arrived at a similar conclusion based on data from the Danish Health-Care Registries by comparing 10,690 patients who underwent ES and ERCP with a similar group of patients who underwent ERCP but not an ES procedure. The highest cholangiocarcinoma incidence rate was observed during the first year after ERCP and decreased progressively over time. A gradual decrease in the cholangiocarcinoma rate was observed over time after ERCP in patients who underwent a sphincterotomy, suggesting that some of these patients had cholangiocarcinoma at the time of ERCP but were not diagnosed until 2–5 years later, as interpreted by the authors [25]. The authors interpret this observation of similar rates at the most recent follow-up after ERCP as a lack of a causal association between sphincterotomy and cholangiocarcinoma [25].

Prevention of adverse events after ERCP

Post-ERCP pancreatitis (PEP), although not always well defined, has been regarded as a potentially severe complication, with a reported frequency ranging between 1 and 10%. Swahn et al. [32] (Table 2) reported a reduction in the risk of PEP from 3.2 to 2.6% when a rendezvous cannulation technique was employed compared with conventional biliary cannulation [30]. These values are based on the evaluation of 12,718 ERCP procedures performed in patients without any previous ERCP history and were comparable to an OR of 0.5 (95% CI 0.2–0.9, $p=0.02$). Nevertheless, the incidence of this complication is rather low, and the calculated number needed to treat (NNT) is as high as 71 to avoid one case [32]. A recent study by Lubbe et al. [24] also focused on adverse events related to the ERCP procedure (Table 2). Based on national data recorded between 2007 and 2012 from 36,352 ERCP procedures performed in Sweden, including 408 single-operator per-oral cholangioscopy procedures, the incidence of postprocedural adverse events was higher when retrograde intraductal cholangioscopy was used (19.1% vs. 14.0%), which was also true in the multivariate calculation adjusted for confounders [24].

The prevention of PEP by the use of prophylactic pancreatic stenting (PS) was addressed in the recent Swedish 'GallRiks' study by Olsson and coworkers [27], with patient data recorded between 2006 and 2014 (Table 2). Only patients with an intention to cannulate the bile duct (i.e., no intention to cannulate the pancreatic duct) were included. Pancreatic

stents with a diameter > 5 Fr and a length > 5 cm provided better protection against PEP than shorter and thinner stents [27].

The role of prophylactic antibiotics in reducing adverse events after ERCP was evaluated by Olsson et al. [26]. Data from 31,188 ERCPs were analyzed. Postprocedural adverse events occurred in 11.6% of patients when prophylactic antibiotics were employed compared with 14.2% when no antibiotics were offered. While the relative reduction in risk was 26%, the absolute reduction in adverse events by prophylactic antibiotics was modest (2.6%). The subgroups of patients who should be offered prophylactic antibiotics in relation to ERCP remained unclear.

A number of take-home messages were extracted from the population-level studies outlined in Table 3. The Canadian study reported stable ERCP activity in the Alberta region in the 1990s, with a higher age-adjusted ERCP rate in women than in men, which was predominantly explained by a higher age-specific ERCP rate in women younger than 60 years. Additionally, significant differences between provincial health regions were observed. The proportion of therapeutic procedures increased dramatically from 33 to 70% between 1994 and 2001 [39]. During the same period, the proportion of endoscopists performing fewer than 50 sphincterotomies decreased annually from 72 to 40% [39]. Based on information obtained during the 1980s and 1990s from the Manitoba province in Canada, Moffat and coworkers [40] reported an increase in the use of ERCP between 1984 and 2009, a significant shift from diagnostic to therapeutic procedures, and an increasing age of the population undergoing an ERCP. An increasing rate of a biliary indication for ERCP was reported, with a decreasing rate of pancreas disease. Nevertheless, only 2% of the therapeutic ERCPs in 1987 were pancreatitis-related, which increased to 88.9% in 2009.

In the "benchmarking ERCP project" of Austria conducted in 2006, Kapral et al. [7] reported the success (84.8%) and complication rates (12.6%) in their nonselected population compared with those reported elsewhere. Endoscopists with an annual case volume exceeding 50 ERCPs achieved higher success rates and lower overall complication rates. In a Norwegian study [12] covering 11 of the 35 governmental hospitals with an ERCP service during that period, an overall 95% completeness of data, a high proportion of therapeutic procedures (91.6%) and a complication rate of 11.6% with a procedure-related mortality of 1.4% were observed. Morbidity and mortality were predominately related to patient age and comorbidities but also to the annual hospital ERCP volume (notably, a higher risk was encountered in hospitals that performed more than 150 procedures annually) and type of intervention. In a smaller study based on a community practice in Minnesota/USA, Colton and coworkers [10] reported a proportion of 78.4% therapeutic ERCP procedures. Moreover, a complication rate of 5.0% was reported, and the authors underscored that the technical success rates achieved were consistent with or exceeded the rates recommended by the American College of Gastroenterology Task Force (ASGE) [47].

Discussion

Although true population-based studies on ERCP are rare, the present review provides data on outcomes after ERCP with external validity and reflects the ERCP practice in the larger community. With few exceptions, the identified studies mainly originated from countries with predominantly governmental public health care systems (i.e., Nordic countries, a few European countries, and Canada), where economic incentives had little impact on treatment decisions. The sizes of the series varied and included samples ranging from a few hundred patients [10] to more than 120,000 procedures [31]. We were unable to identify any true population-based study that was published before 1997, which is more than two decades after the ERCP procedure was introduced as a gastrointestinal clinical tool in the early 1970s [1–3].

A few large clinical studies on ERCP have set the standard for ERCP as a diagnostic tool and eventually as a valuable therapeutic tool in the management of pancreatic and biliary benign and malignant diseases [5, 8, 11, 48]. Moreover, results from some RCTs have been published, focusing on post-ERCP complications [48], or more specifically on the risk of post-ERCP pancreatitis [49–51], as well as whether wire-guided cannulation [52] or pharmacological prevention [53] reduces this risk. The outcomes of these studies have been analyzed in a number of systematic reviews and meta-analyses [50, 51, 54–58]. While this core knowledge is valuable and important, the external validity of these studies and meta-analyses are limited, and the outcomes should not be implemented and extrapolated into routine practice without considering that these studies were performed under very specific circumstances [16]. Therefore, the information provided by national population-based registries is considered valuable and relevant.

The National Patient Registries of the Nordic countries are essentially complete in terms of epidemiologic aspects, including basic demographics and hospital admissions [59]. The accuracy regarding specific diagnoses and procedures may be hampered by incomplete reporting or registration, but is generally regarded to be of high quality. Data retrieval through cross-linking with national cancer registries, which are based on a mandatory reporting of every new case, improves the quality of the merged databases [59, 60]. Nevertheless, the quality of the clinical registries relies on strict and complete reporting, as well as on a high and complete rate of follow-up (i.e., 30-day follow-up) to capture adverse

events encountered after discharge from the hospital [16]. Recently, these aspects have been addressed by validation of the national 'GallRiks' database in Sweden [22]. Results reported from the Manitoba province in Canada based on Manitoba Health [40] should be regarded as reliable. These administrative databases have proven to be highly accurate for population-based validation cohorts, including colon cancer [61] and diabetes [62]. In a British study [20], the hospital episode statistics (HES) for 2006–2007 and 2007–2008 were linked to the statutory death register. Data are reported from all NHS trusts in England. While challenges remain regarding the validation of the quality of these data, in-hospital mortality has been evaluated based on HES data in previous studies [20, 63].

Many studies utilize mortality as the ultimate outcome measure. Although mortality may be a very valid measure, particularly in population-based studies, the interpretation of mortality in this patient group has some issues. High-risk groups with serious cardiovascular diseases or cancers obstructing the bile ducts are overrepresented, leading to relatively high 30-day mortality rates. Some studies are limited to in-hospital mortality, making comparisons with studies that provide follow-up data unreliable, whereas other studies focus on success rates. Furthermore, some studies do not clearly delineate when an ERCP is recorded as an intended procedure (i.e., and not "discarded as an unsuccessful attempt"). Thus, the total number of intended ERCPs in the denominator may not be well defined, and consequently the calculated frequencies of adverse events may be biased. Post-ERCP pancreatitis is also an important measure of safety, but the lack of criteria to distinguish a deterioration of pancreatitis already present prior to the procedure and a new case of pancreatitis caused by the ERCP makes this outcome difficult to assess.

Over time, the indications for ERCP have changed from a diagnostic tool to a mainly therapeutic procedure. This evolution has been paralleled by the introduction of newer imaging modalities (i.e., MRI) for the diagnosis of the pathology of the biliary tree and the pancreatic duct. Based on observations from our identified registry studies, this change has occurred worldwide, although with a slightly different rate. Further progress in the indications is evolving and will likely be prompted by novel technical developments that will overcome current obstacles or restrictions. A challenge remains concerning the prediction of adverse effects in more or less fragile patients undergoing ERCP. A number of criteria and classification systems have been developed. Researchers have not yet determined whether a single classification system is better than another, but a systematic approach to important clinical decision-making is warranted [64].

Higher complication rates were observed in academic centers, most likely because of differences in the case mix of patients and a greater number of therapeutic procedures. The trainee case load correlated with the ERCP success rate, but not with procedure-related complications [65].

The risk of cancer after endoscopic sphincterotomy has been reported in a number of studies [23, 29, 30]. Constant exposure to intestinal contents in the biliary duct after a sphincterotomy may cause chronic inflammation, which, theoretically, might be carcinogenic in the long term. The possibility that inflammation is a trigger for cancer has been confirmed in several studies and has been the subject of many studies on different organ systems. However, since the suspicion of a cancer is a common indication for ERCP, clinicians are not able to easily distinguish between pathologies that are already present in the bile ducts and conditions that have developed as a result of the sphincterotomy.

A strength of this study is the focus on the scientific literature that most likely reflects the routine clinical practice of ERCP, as reported to population registries. Thus, the provided observations were obtained from general unselected populations treated in routine practice according to current standards of clinical care.

Additionally, some limitations of registry studies should be considered when interpreting the reported observations. The validity of the diagnosis and procedure codes may pose a challenge, and the categorization of patients and subgroups relies on a suggested high quality and the consistent use of proper coding manuals (i.e., International Classification of Diseases (ICD) codes) or specific data manuals designed for a particular database (e.g., 'GallRiks' in Sweden [22]). Thus, details regarding patient's comorbidity and relevant procedure-related adverse events may vary between studies, and differences in the completeness of reporting and follow-up likely affect reported outcomes [16, 22]. As recently reported [16, 41, 43], many population-based databases are often restricted to in-hospital ERCPs, which should be considered when values are compared. Moreover, formal obstacles (e.g., legislation, database structure, definitions, and the type and number of variables) that may hamper access to important clinical information may prevent comparisons between countries [36, 46, 66].

Some key findings of this review are displayed in Table 3. How to judge the importance, relevance, and possible consequences of these findings may be questioned. Nevertheless, we think a number of clues could be provided.

Most likely, in a global setting, ERCP services are improving. Studies employing different designs (i.e., innovational studies, early phase II/III studies, RCTs, and registry studies on a population level) should be planned and completed to provide insights into various aspects of the ERCP procedure and the quality of care. How a nationwide registry can be used to monitor activity and focus on results should be obvious; participating in research may stimulate a fruitful competition between centers. Regular feed-back (i.e., annually) elucidates results of individual centers against a national

average, or a quality level that has been agreed upon in consensus. Moreover, possible differences between hospital levels (i.e., university hospitals/academic institutions, nonteaching/county hospitals, and district general hospital) could be provided, to enable adjustments with regard to referral patterns, resource allocations or organization of health care in general to improve the service. Although improvements may be partially explained by a "Hawthorne effect" (i.e., improvements as the result of monitoring per se), this is indeed not a "quick fix" [67]. However, national figures based on a relevant and consistent prospective reporting of high quality would likely be helpful, as demonstrated by a number of reports cited in this study [20, 22, 31, 43].

Data from national registries may have a direct impact on clinical management of this group of patients, including treatment approaches. An example from Sweden is the shift to intraoperative ERCP when common bile duct stones were encountered by intraoperative cholangiography, as reported by Swahn and coworkers in 2013 [32]. This approach was introduced more than 10 years earlier [68]. Moreover, the use of prophylactic antibiotics in relation to ERCP remains a matter of debate. Nevertheless, figures from the population-based study by Olson et al. showed only a modest absolute risk reduction of 2.6% when antibiotics were employed, and they recommend further research to be done in order to more conclusively define a high-risk group where routine use of antibiotics is warranted [26].

The Japanese endoscopic community, with a number of leading scientists and clinicians within the field of gastrointestinal endoscopy, has recently decided to embark on a nationwide reporting of their endoscopy activity [69]. We should have clear guidelines for our current standards of patient care, including the ERCP service, to achieve further developments and advances [67]. In that context, the collection of valuable information and core knowledge from routine clinical practice as reported to population-based databases may help improve patient care from best evidence to best practice [17].

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Compliance with ethical standards

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