Is an endoscopic examination associated with transfusion-transmissible infections? A systematic review and meta-analysis

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BACKGROUND: The purpose of a donor medical questionnaire is to identify the blood donor's history relative to the current known blood-safety risks. A temporary deferral from blood donation after an endoscopic examination is enforced because of the reusable nature of the endoscope and close contact with the inner body. The objective of this systematic review was to find the best available evidence on the association between an endoscopic examination and the risk of transfusion-transmissible infections.

METHODS: Studies from five databases investigating the link between an endoscopic examination and transfusion-transmissible infections (hepatitis B virus, hepatitis C virus, human immunodeficiency virus infection, *Treponema pallidum*) were retained and assessed independently by two reviewers. The association between endoscopy and transfusion-transmissible infections was identified by conducting meta-analyses and calculating pooled effect measures (odds ratios and 95% confidence intervals). The Grading of Recommendations, Assessment, Development, and Evaluation methodology was used to assess the quality of evidence.

RESULTS: We identified 7571 references and finally included 29 observational studies. A significant association between an endoscopic examination and hepatitis B virus infection (pooled odds ratio [OR], 2.21; 95% confidence interval [CI], 1.26-3.86; $p = 0.005$) or hepatitis C virus infection (pooled OR 1.76, 95% CI, 1.45-2.14; $p < 0.00001$) was found. The level of evidence was considered as "very low" due to the type of study design (i.e., observational) and indirect study populations (i.e., no blood donor populations).

CONCLUSION: An endoscopic examination is associated with an increased hepatitis B virus or hepatitis C virus infection risk. Further high-quality trials are required to formulate stronger evidence-based recommendations on endoscopic examination as a blood donor deferral criterion.

The safe transfusion of blood and blood products helps to save millions of lives every year. However, in many countries, demand far exceeds supply, and blood services face the constant challenge of making sufficient blood available while also ensuring its quality and safety. In 2016, more than 40 years after the first World Health Assembly resolution (WHA28.72) addressed the issue of blood safety, equitable access to safe blood and blood products, and the rational and safe use of blood transfusion, there are still major challenges throughout the world, and many patients who require transfusion do not have timely access to safe blood.[1]

ABBREVIATIONS: GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; TTI(s) = transfusion-transmitted infection(s).

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This work was supported by funding from the Foundation for Scientific Research of the Belgian Red Cross.

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Received for publication July 20, 2017; revision received October 10, 2017; and accepted October 10, 2017.

doi:10.1111/trf.14416

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TRANSFUSION 2017;00;00–00

An important element in the development of voluntary blood donor eligibility criteria throughout the world has been the attention given to minimizing the risk to recipients of donated blood, primarily the risk of infection by transfusion-transmitted diseases, such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), and *Treponema pallidum*.[2] Therefore, it is routine to complete a donor medical questionnaire and a physical examination before every blood donation to identify the donor's history relative to current, known blood-safety risks.[3]

One of the potential risks addressed in the donor medical questionnaire is whether the blood donor has a (recent) history of endoscopic procedures. Because of its reusable nature and close contact with the inner body, it is hypothesized that an endoscope can pose a threat to the blood supply by serving as a means of transmitting different viruses.[4,5] A European Directive in 2004 demanded a deferral period of 6 months (or 4 months when a nucleic acid test for HCV has proved negative) for every person who undergoes a flexible endoscopic examination.[6]

However, the scientific basis for this temporary deferral criterion is still unclear. As proposed by European blood directives, it is recommended to use an evidence-based approach for basing donor selection criteria on solid scientific evidence.[7]

Therefore, the objective of this systematic review was to identify all available scientific evidence on the association between an endoscopic examination and the risk of infection by transfusion-transmittable diseases. We hypothesized that individuals who undergo an endoscopic examination have an increased risk of a transfusion-transmitted infection (TTI).

MATERIALS AND METHODS

We carried out a systematic literature review according to a predefined protocol.[8] We planned and reported the systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Appendix S1, available as supporting information in the online version of this paper).[9]

Data sources and searches

A literature search was performed in CENTRAL, MEDLINE (via the PubMed interface), Embase (via Embase.com), CINAHL (using the EBSCOhost interface), and Web of Science for eligible studies from the time of inception of the database until December 2016. We developed sensitive search strategies for each database, including the use of index terms and free text terms (Appendix S2, available as supporting information in the online version of this paper). Search yields were exported to a citation program (Reference Manager, version 12), duplicates were discarded, and title and abstract screening was initiated.

Study selection

Studies were eligible for inclusion if they answered the following PICO question: "In adults (*population*), is an endoscopic examination (*intervention/risk factor*) a risk factor for transfusion-transmissible infections (TTIs) (*outcome*) compared with no endoscopic examination (*comparison*)?" The review was restricted to original articles published in English, French, or Dutch. Other relevant foreign-language references were assessed if an English, Dutch, or French title or abstract was available. Full texts of potentially relevant articles were reviewed according to the following inclusion and exclusion criteria:

- Population: *Inclusion*, adults; *exclusion*, children;
- Intervention/risk factor: *Inclusion*, an endoscopic examination that was not limited to 1) the type of examination (e.g., duodenoscopy, laparoscopy, rhinoscopy), 2) the reason for examination (e.g., diagnostic or surgery), and 3) the type of instrument that was used (e.g., rigid vs. flexible endoscope); *exclusion*, otoscopy and capsule endoscopy;
- Comparison: *Inclusion*, no endoscopic examination;
- Outcome: *Inclusion*, markers of TTIs from the following pathogenic microorganisms in the blood: HIV, HBV, HCV, and *T. pallidum* (causing syphilis); and
- Study design: *Inclusion*, experimental studies (randomized controlled trials, controlled clinical trials, before-and-after studies) and observational studies (cohort studies and case-control studies); *exclusion*, noncontrolled studies, cross-sectional studies without appropriate analysis (i.e., case-control analysis), case reports, case series, letters, comments, opinion pieces, and narrative reviews.

Two reviewers independently performed the title and abstract screening followed by the full text assessment according to these inclusion and exclusion criteria. Disagreements were resolved by discussion or by consulting a third reviewer.

Data extraction and quality assessment

Data concerning study design, population characteristics, risk factor (i.e., endoscopic examination), outcome measures (markers of TTIs expressed as a risk ratio, odds ratio, or incidence ratio), and study quality were extracted independently by two reviewers. In case studies that reported both unadjusted and adjusted effect measures, only the adjusted effect measures were extracted. The methodological quality of included studies as well as the overall level of the body of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[10] GRADE considers limitations

in study design (risk of bias) of the included studies, inconsistency between the different studies (caused by differences in populations, interventions, or outcomes), indirectness (of population, intervention, or outcome), imprecision, and publication bias. Publication bias was assessed by visual inspection of funnel plots and by formal testing with linear regression analysis of funnel plot symmetry using the R statistical software package (R Foundation for Statistical Computing). The quality of the evidence can be downgraded for each of the previous quality criteria and finally results in a high, moderate, low, or very low level of evidence.

Meta-analysis

Effect measures of association between endoscopy and markers of TTIs were expressed as odds ratios (ORs) with or without adjustment for confounding factors (i.e., adjusted and unadjusted ORs, respectively). By calculating the log[OR] and its corresponding standard error (standard error = [upper limit of the 95% confidence interval (CI) − lower limit of the 95% CI]/3.92), a random-effects model was constructed using the generic inverse variance method.[11] First, the effect measures for each outcome (HIV, HBC, HCV, *T. pallidum*) were pooled (one effect measure per study) in one model according to the type of study design. Second, different subgroup analyses were conducted to explain potential heterogeneity across studies. Subgroup analyses were performed according to: 1) the type of outcome measure (acute vs. chronic HBV infection); 2) the type of statistical analysis (adjusted vs. unadjusted effect measures); 3) the time of publication (before the European Directive [before 2004] vs. after the European Directive [2004 and later]); 4) Centers for Disease Control and Prevention statistics used to define HBV and HCV prevalence for each country,[12,13] comparing higher prevalence regions (>2% for HCV infection and >5% for HBV infection) with lower prevalence regions (≤2% for HCV infection and ≤5% for HBV infection); and 5) the location where the study was conducted (i.e., European vs. non-European countries).

The (pooled) results were summarized in a forest plot, which is the graphic output of a meta-analysis that includes all studies with their (pooled) estimate and CI, together with results from an evaluation of heterogeneity.[14] Heterogeneity was evaluated by the visual assessment of the overlap in CIs in the forest plot, the chi-square test (if $p < 0.10$), and the I^2 statistic, which estimates the percentage of total variation between studies caused by heterogeneity rather than chance. The following thresholds for the interpretation of I^2 can serve as a rough guide: 0 to 40%, may not be important; 30 to 60%, may represent moderate heterogeneity; 50 to 90%, may represent substantial heterogeneity; and 75 to 100%, considerable heterogeneity.[15] Review Manager 5.3 was used to perform meta-analyses. A p value less than 0.05 was considered significant.

RESULTS

Study selection

The systematic literature search resulted in a total of 7571 citations, which were scrutinized independently by two reviewers. Figure 1 represents the study-selection process used in the systematic review. We eventually included 29 observational studies (three cohort studies and 26 case-control studies). Ten of the case-control studies (34%) were matched for age, sex, donation date, area of residence, and/or number of chronic diseases; whereas the other 16 case-control studies (66%) were unmatched. Five studies (17%) were published in the past 5 years (2013-2017), six (21%) were published within 5 to 10 years (2008-2012), seven (24%) were published within 10 to 15 years (2003-2007), seven (24%) were published within 15 to 20 years (1998-2002,) and four (14%) were published greater than 20 years ago. The majority of included studies (76%) were conducted in the European region (n = 11: France, n = 6; Italy, n = 3; Turkey, n = 1; Poland, n = 1) and in the Eastern Mediterranean region (n = 11: Iran, n = 5; Egypt, n = 4; Saudi Arabia, n = 1; Lebanon, n = 1). Three studies were performed both in the South-East Asia region (South Korea, n = 3) and in the Western Pacific region (n = 3: China, n = 2; Australia, n = 1), only one study was performed in the region of the Americas (Brazil, n = 1), and no studies were done in the African region. The type of endoscope was not explicitly described in 22 studies; whereas digestive endoscopy (n = 4), gastrointestinal endoscopy (n = 2), and perendoscopic biopsy (n = 1) were used in seven studies. All articles described different TTIs as risk factors for an endoscopic examination. Eighteen articles focused on HCV infection, nine described HBV infection as a possible risk factor, and two investigated the risk factors for both HBV and HCV. No articles documented the association between an endoscopic examination and HIV or *T. pallidum*. Details on the characteristics of the included studies are provided in Table 1.[16-44]

Association between endoscopic examination and HBV infection

Case-control studies

A meta-analysis of nine case-control studies revealed a significant association between HBV infection and endoscopic examination (pooled OR, 2.21; 95% CI, 1.26-3.86; p = 0.005), with a large amount of heterogeneity between trials ($I^2 = 90\%$) (Fig. 2).[17,19,20,27,35,40,45-47] When excluding the study by Jahangirnezhad and colleagues, heterogeneity (I^2) was reduced from 90 to 56%. Therefore, this study was excluded from the different subgroup analyses. A first subgroup analysis on the type of HBV infection measure indicated that this association was still present in the

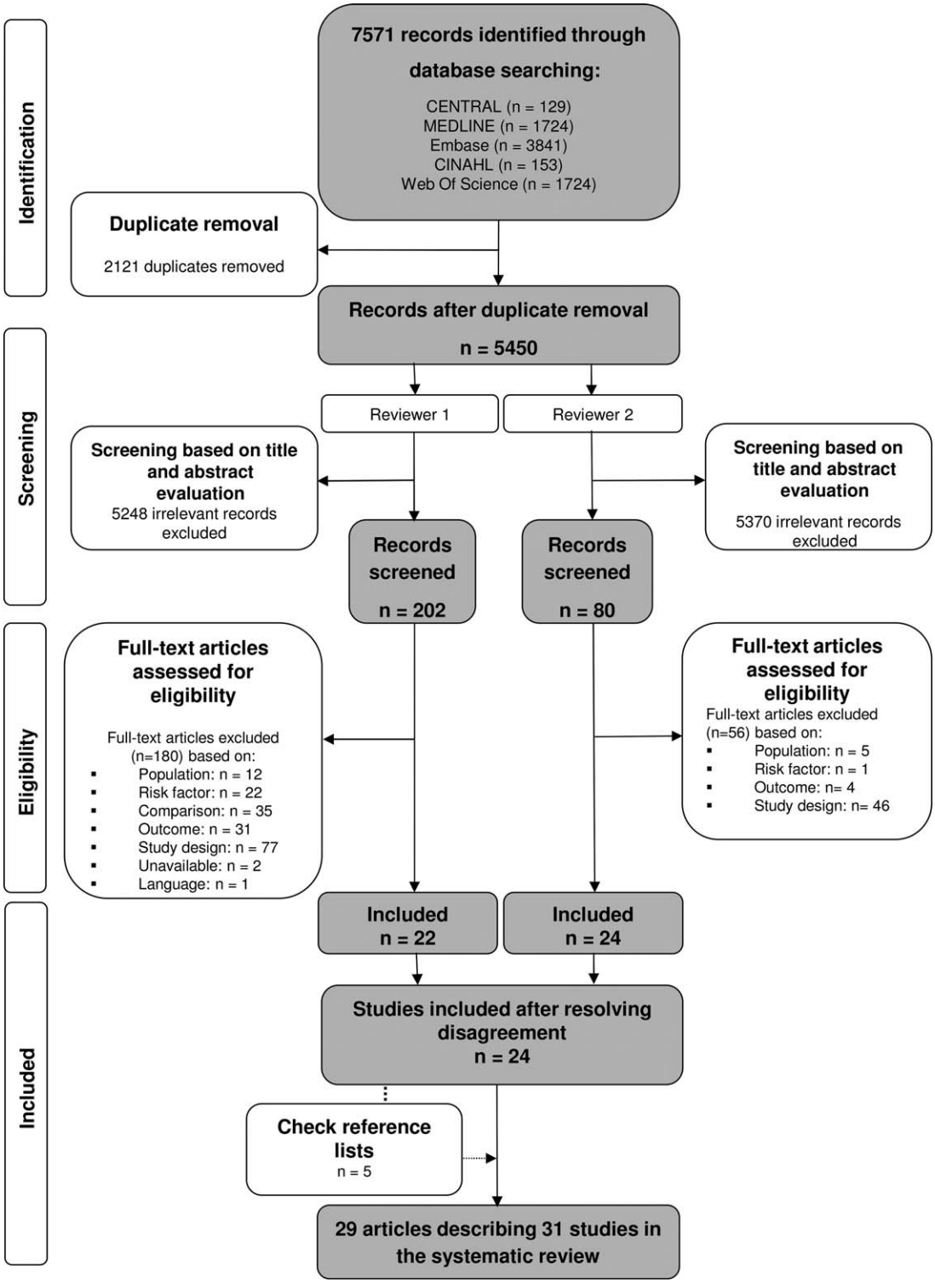

Fig. 1. Study identification and selection process of the systematic review.

studies that did not explicitly define the HBV infection outcome (e.g., acute or chronic; pooled OR, 1.43; 95% CI, 1.03-1.98; $p = 0.03$) or had a specific chronic HBV infection outcome (OR, 86; 95% CI, 31.16-237.36; $p < 0.00001$). However, one Italian study that explicitly investigated an "acute HBV infection" could not demonstrate this association (OR, 1.40; 95% CI, 0.90-2.18; $p = 0.14$). Subgroup differences were significant ($p < 0.00001$) (Fig. S1, available as supporting information in the online version of this paper). A second subgroup analysis compared studies

TABLE 1. Characteristics of the included studies

First author and year; country	Study design	Population	Risk factor	Outcome measure
Alavian 2002[16]; Iran	Observational: Case-control study (unmatched)	First-time blood donors referred to the Iranian Blood Transfusion Organization from April 1996 to June 1998: 193 HCV-positive donors (cases) and 196 HCV-negative donors (control)	Endoscopy	HCV infection
Al-Thaqafy 2013[17]; Saudi Arabia	Observational: Case-control study (unmatched)	400 Male Saudi National Guard Personnel (SANG) soldiers working in Jeddah during January 2009; 53 positive for hepatitis B core antibody (anti-HBc) (cases) vs. 447 negative for anti-HBc (controls)	Endoscopy	HBV infection
Andrieu 1995[18]; France	Observational: Case-control study (unmatched)	2607 Hospitalized patients in the Gastroenterology Unit who filled out a questionnaire about risk factors (1 April to 30 June 1991): 174 HCV-positive cases and 2433 HCV-negative controls	Perendoscopic biopsies	HCV infection
Ansari-Moghaddam 2016[19]; Iran	Observational: Case-control study (unmatched)	654 Male municipal employees in Zahedan (south-eastern Iran) tested for HBV in 2013; 178 municipal solid waste workers, 293 municipal employees not exposed to waste, and 183 Zahedan municipality drivers (overall mean age, 41.6 $\pm$ 9.1 y); 20 positive for hepatitis B surface antigen (HBsAg) (cases), 634 negative for HBsAg (controls)	Endoscopy	HBV infection
Baddoura 2002[20]; Lebanon	Observational: Case-control study (unmatched)	Lebanese population presenting to all laboratory units in the country over a 2-week period for whatever medical reason (unknown period, but before April 2001); 546 HBV-positive, 20 HCV-positive, and 2327 HBV-negative controls	Gastrointestinal endoscopy	HBV and HCV infection
Barut 2011[21]; Turkey	Observational: Case-control study (unmatched)	Individuals referred to Gaziosmanpasa University Hospital outpatient clinic of Infectious Diseases and Clinical Microbiology between January 2005 and March 2008 (cases); patients who applied to the same hospital or to internal medicine outpatient clinic with diseases other than hepatitis, or the adult female patients who were stationary-monitored at Tokat Maternity and Child Care Hospital: 193 HCV-positive cases and 190 HCV-negative controls	Endoscopy	HCV infection
Chlabicz 2004[22]; Poland	Observational: Case-control study (matched for age and sex)	194 HCV-positive cases vs. 275 controls selected between 1 June 1998 and 31 December 2002 in the Department of Infectious Diseases	Endoscopy	HCV infection
Ciancio 2005[23]; Italy	Observational: Cohort study	9008 Patients who underwent gastroscopy at three endoscopic units between January 1999 and December 2002 and 51,230 controls (endoscopy-negative group; healthy blood donors who donated blood at two blood banks in the same area and during the same period)	HCV infection	HCV infection
Delarocque-Astagneau 2007[24]; France	Observational: Case-control study (matched for age, sex, and study population)	Repeat blood donors who seroconverted between 1998 and 2001 (with a final negative third-generation test reported in 1995 or later) (Cases I) and seroconverters referred to hepatology departments in 2000 through 2001 (Cases II): 64 cases in total and 227 controls	Digestive endoscopy	HCV infection

Table 1: *Continued*

First author and year; country	Study design	Population	Risk factor	Outcome measure
el-Sadawy 2004[25]; Egypt	Observational: Case-control study (matched for area of residence)	367 Cases vs. 1055 controls in urban and rural areas of Sharqia Governate, Egypt; no period of data collection was reported	Endoscopy	HCV infection
Habib 2001[26]; Egypt	Observational: Case-control study (unmatched)	Households from a village in the Nile Delta (Aghour El Soughra); 23 cases and 3993 controls selected in 1997	Endoscopy	HCV infection
Jahangirnezhad 2011[27]; Iran	Observational: Case-control study (unmatched)	Individuals referred to the Gastrointestinal Department, Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences from October 2009 to June 2010 (cases) or patients referred to the Gastrointestinal Clinics (controls): 272 cases with chronic HBV vs. 288 HBV-negative controls	Endoscopy	HBV infection
Kandeel 2012[28]; Egypt	Observational: Case-control study (matched for age and sex)	Between June 2007 and September 2008, cases and controls from two infectious disease hospitals in Cairo and Alexandria were enrolled: 86 cases with acute hepatitis and 287 controls (hospital visitors not living in the case-patient households)	Endoscopy (within 6 months before interview)	HCV infection
Karmochkine 2006[29]; France	Observational: Case-control study (matched for sex, age, geographic residence, and no. of chronic diseases)	450 HCV-seropositive patients with no history of transfusion or intravenous drug use referred through a nationwide network of physicians working in 57 departments of internal medicine, hepatology, or infectious diseases vs. 757 controls selected from the general population using a computer-generated list originating from the telephone book (between November 1997 and June 2001)	Digestive endoscopy	HCV infection
Kim 1996[30]; Korea	Observational: Case control study (matched for age and sex)	64 HCV-positive cases vs. 128 controls at the Asan Medical Center (between September 1993 and February 1994)	Endoscopy	HCV infection
Kim 2002[31]; Korea	Observational: Case-control study (unmatched)	178 HCV-positive cases vs. 226 controls (spouses of HCV-polymerase chain reaction-positive patients and hospital visitors from a control hospital, between September 1994 and December 1998)	Endoscopy	HCV infection
Liu 2009[32]; China	Observational: Case-control study (matched for age, sex, and place of residence)	69 HCV-positive cases vs. 207 controls from eight villages in four counties of Anyang, Henan Province, China (2006-2008)	Gastroscopy	HCV infection
Maugat 2003[33]; France	Observational: Case-control study (unmatched)	91 Cases vs. 853 controls from interventional radiology wards in 6 university hospitals in Paris between 1998 and 1999	Endoscopy	HCV infection
Medhat 2002[34]; Egypt	Observational: Case-control analysis (unmatched)	Cases and controls from a village in Upper Egypt with a moderately high prevalence (8.7%) of antibodies to HCV; 523 HCV-positive cases vs. 5510 HCV-negative controls	Endoscopy	HCV infection
Mele 2001[35]; Italy	Observational: Case-control study (unmatched)	Data from 1994 to 1999 in the National Health Institute of Italy database: 3120 individuals with HBV and 1023 with HCV (cases) vs. 7158 with hepatitis A virus (controls)	Endoscopy	HBV and HCV infection
Merle 1999[36]; France	Observational: Case-control study (matched for age and sex)	178 Cases vs. 319 controls (both cases and controls living in Fecamp, France); cases were collected between April 1994 and September 1996	Digestive endoscopy	HCV infection

Table 1: *Continued*

First author and year; country	Study design	Population	Risk factor	Outcome measure
Rachail 1977[37]; France	Observational: Cohort study	1114 Patients who underwent endoscopy and 2903 who did not; date of recruitment of study participants is unclear	HBV	HBV infection
Seong 2013[38]; Korea	Observational: Case-control study (unmatched)	1173 Cases vs. 534 controls (all controls had liver diseases not caused by HCV or HBV and were enrolled in the liver clinics of the same hospitals as the cases during the same period [i.e., university hospitals] from January 2007 to December 2011)	Endoscopy (for diagnostic purposes)	HCV infection
Sali 2005[39]; Iran	Observational: Case-control study (matched for age)	Individuals who came to Karaj Hepatitis Center between February 2001 and December 2003: 500 cases with chronic HBV and 434 controls (negative for HBV, HCV, and HIV) selected by simple random sampling	Endoscopy	HBV infection
Tolentino 2008[40]; Brazil	Observational: Case-control study (unmatched)	176 Patients with inflammatory bowel disease (between May 2002 and November 2004); 30 HBV-positive cases vs. 146 HBV-negative controls	Endoscopy (i.e., digestive endoscopy or rectosigmoidoscopy)	HBV infection
Vickery 2009[41]; Australia	Observational: Case-control study (unmatched)	100 Cases vs. 2019 controls from the Royal Prince Alfred Hospital from July 1999 to December 2001	Endoscopy	HCV infection
Villa 1984[42]; Italy	Observational: Cohort study	581 HBV-negative patients who underwent endoscopic evaluation (gastroscopy, laparoscopy, colonoscopy, or endoscopic retrograde cholangiopancreatography) vs. 100 HBV-negative controls admitted in the same unit in the same period who did not undergo endoscopic evaluation (April to October 1981); patients who had undergone endoscopy in the previous 6 months were excluded from the study	HBV infection	HBV infection
Zhong 2016[43]; China	Observational: Case-control study (matched for age, sex, and donation date)	265 HBsAg-positive Chinese blood donors (63% male, 53.2% ages 18-34 y, 46.8% ages 35-55 y) and 530 seronegative Chinese donors (63% male, 53.2% ages 18-34 y, 46.8% ages 35-55 y)	Endoscopy	HBV infection
Ziaee 2016[44]; Iran	Observational: Case-control study (unmatched)	85 HBsAg-positive Iranian cases (52% male; 20% 15-34 y, 45% (35-54 y, 20% 55-70 y) and 5150 seronegative controls	Endoscopy	HBV infection

with unadjusted ORs versus those with ORs adjusted for confounding variables, such as age, sex, and history of blood transfusion. HBV infection was significantly associated with endoscopic examination in the studies that used adjusted ORs (pooled OR, 1.76; 95%CI, 1.28-2.43; $p = 0.0005$), whereas no association was reported in the studies with unadjusted ORs (pooled OR, 1.12; 95% CI, 0.79-1.58; $p = 0.08$)). Subgroup differences tended to be significant ($p = 0.06$) (Fig. S2, available as supporting information in the online version of this paper). A third subgroup analysis compared studies conducted in low HBV prevalence regions ($n = 7$ studies) versus those conducted in high HBV prevalence regions ($n = 1$ study) and reported significant associations in both groups (low HBV prevalence regions: pooled OR, 1.34; 95% CI, 1.01-1.79; $p = 0.05$; high HBV prevalence regions: pooled OR, 2.17; 95% CI, 1.04-4.53; $p = 0.04$). Subgroup differences were not significant ($p = 0.23$) (Fig. S3, available as supporting information in the online version of this paper). A fourth subgroup analysis compared studies that were published before the European Directive (before 2004; $n = 2$) with those published after the European Directive (2004 and later; $n = 7$). Studies published before 2004 reported a significant association between HBV infection and an endoscopic examination (pooled OR, 1.43; 95% CI, 1.13-1.81; $p = 0.003$), whereas no association was reported in the studies published during or after 2004 (pooled OR, 1.47; 95% CI, 0.95-2.29; $p = 0.08$). Subgroup differences were not significant ($p = 0.90$) (Fig. S4, available as supporting information in the online version of this paper). In a final subgroup analysis, data from one European country (i.e., Italy) were compared with data from seven non-European

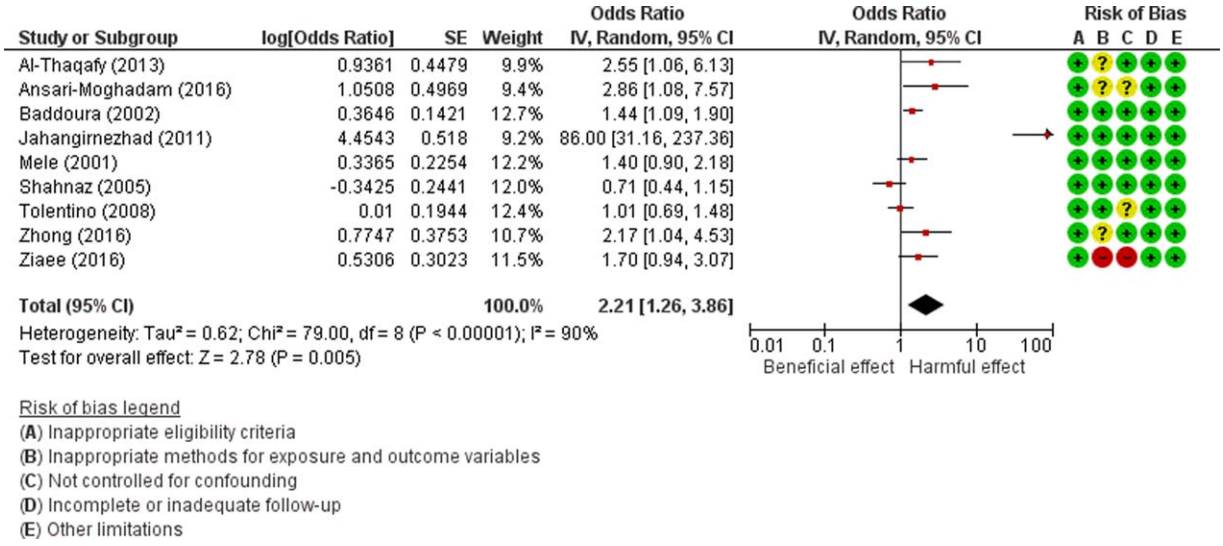

Fig. 2. Study-specific ORs representing the association between an endoscopic examination and HBV infection in case-control studies. Each dot represents the OR of the respective study together with the 95% CI. The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis. low risk of bias, High risk of bias, unclear. [Color figure can be viewed at wileyonlinelibrary.com]

countries. A significant association was reported in the non-European countries (pooled OR, 1.43; 95% CI, 1.06-1.98; p = 0.03) compared with the Italian study, which reported no significant association (OR, 1.40; 95% CI, 0.90-2.18; p = 0.14) Subgroup differences were not significant (p = 0.54) (Fig. S5, available as supporting information in the online version of this paper). Overall, heterogeneity between trials was not further reduced in the subgroup analyses.

Cohort studies

One cohort study (published in 1984) in a gastroenterology unit (University of Modena, Italy) found no association between HBV infection and endoscopic examination (gastroscopy, laparoscopy, colonoscopy, or endoscopic retrograde cholangiopancreatography; OR, 0.45; 95% CI, 0.04-5.06; p = 0.52).[42] A second cohort study (published in 1977) in a French hospital concluded that a negligible danger of contamination by HBV was present in patients who underwent digestive endoscopy (gastroscopy, laparoscopy, rectoscopy, liver biopsy, or colonoscopy). However, that conclusion could not be verified by formal statistical testing due to a lack of data.[37]

Association between endoscopic examination and HCV infection

Case-control studies

A meta-analysis of 17 case-control studies showed a significant association between HCV infection and endoscopic examination (pooled OR, 1.76; 95% CI, 1.45-2.14; p < 0.00001) with a moderate amount of heterogeneity between trials ($I^2 = 47\%$) (Fig. 3).[16,18,21,22,24-26,28-34,36,38,41] The different subgroup analyses uniformly confirmed this association statistically but did not further reduce the heterogeneity (Figs. S6-S10, available as supporting information in the online version of this paper).

Cohort studies

One prospective Italian study in a cohort of patients who underwent endoscopy and a cohort of blood donors demonstrated that digestive endoscopy was not a major risk factor for the transmission of HCV (OR, 0.51; 95% CI, 0.03-8.67; p = 0.64).[23]

Level of evidence

All included studies were observational and thus had an initial low quality level of evidence (according to the GRADE approach). The risk of bias for each included study is detailed in the right in Figs. 2 and 3, and detailed information is provide in Table S1 (available as supporting information in the online version of this paper). A low risk of bias was present in almost all studies (approximately 90%) for the items Inappropriate eligibility criteria and incomplete and inadequate follow-up. There were no other limitations. The two other risk-of-bias items were less frequently judged as having a low risk of bias: Inappropriate methods for exposure and outcome variables (low risk of bias in 30% of the studies vs. 50% [unclear] and 20% [high risk of bias]) and studies not controlled for confounding factors (low risk of bias in 70% of studies vs. 10% [unclear] and 20% [high risk of bias]). When the scores for all risk-of-bias items were collated, no

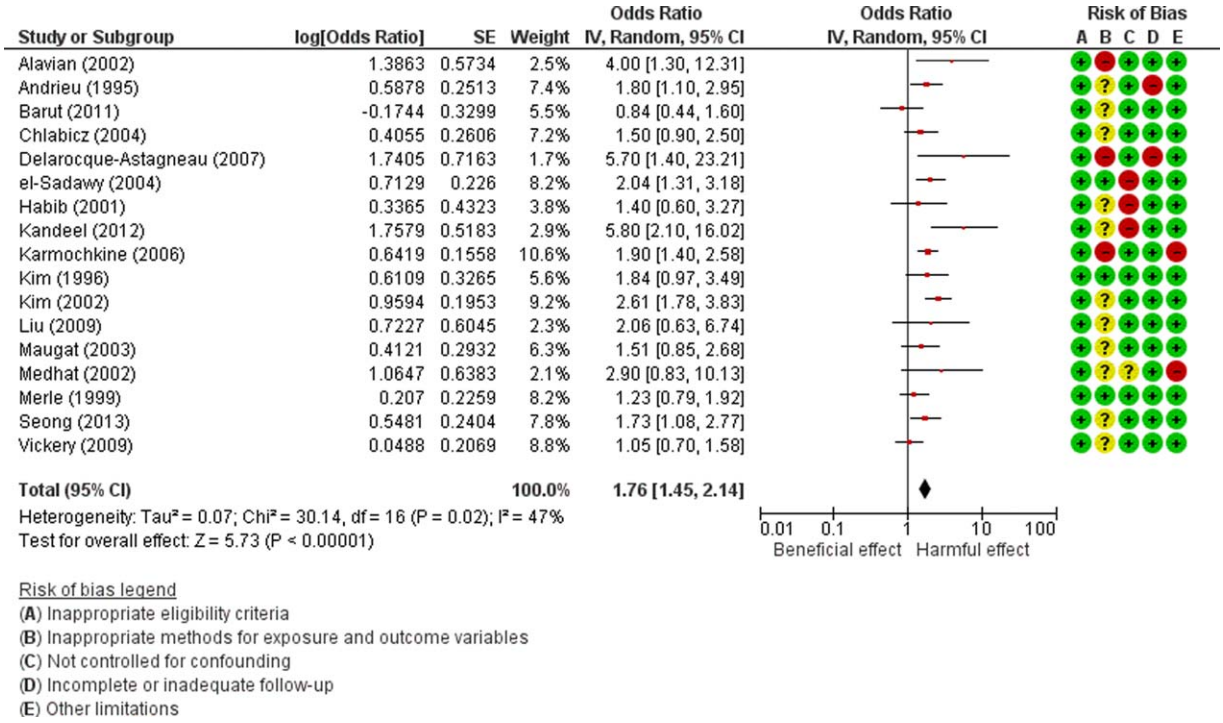

Fig. 3. Study-specific ORs representing the association between an endoscopic examination and HCV infection in case-control studies. Each dot represents the OR of the respective study together with the 95% CI. The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis. low risk of bias, High risk of bias, unclear. [Color figure can be viewed at wileyonlinelibrary.com]

downgrading for risk of bias was considered. Furthermore, no strong indication for imprecise results was present. Because heterogeneity between trials was moderate ($I^2 = 56\%$ for HBV studies [when excluding one outlier] and $I^2 = 47\%$ for HCV studies), and most individual effect measures (ORs) were less than 1 (harmful effect), no downgrading for inconsistency was applied. Visual inspection might demonstrate publication bias (i.e., funnel plot asymmetry) (Figs. S11 and S12, available as supporting information in the online version of this paper). However, no evidence of publication bias was found based on the linear regression test of funnel plot asymmetry ($p = 0.09$ for HBV studies; $p = 0.24$ for HCV studies). Indirectness due to study population was addressed, because none of the studies (except three[16,24,46]) included blood donor populations. Therefore, the strength of the body of evidence (for the association between endoscopic examination with HBV and with HCV infection) was downgraded from low to very low.

DISCUSSION

The current systematic review identified 29 observational studies that investigated the association between endoscopy and TTIs. We observed that an endoscopic examination was significantly associated with HBV and HCV infection (only in the case-control studies, and not in the cohort studies). No studies were identified that linked an endoscopic examination with HIV infection or with *T. pallidum*. The quality of the evidence can be considered as very low because of the study type (observational studies) and the indirect population (no blood donor populations).

Our systematic review can be considered as relevant in terms of policy and may be useful for practice. To date, two systematic reviews concerning specific endoscopic examination and TTIs have been published. First, Morris and coworkers conducted a systematic review in 2005 but restricted the research question to gastrointestinal endoscopy and blood-borne viruses. Those authors screened only three databases (MEDLINE, Embase, and The Cochrane Library) and limited their search to full English-language texts. In addition, they did not conduct a meta-analysis and included study designs of lower quality (i.e., case series and case reports). The group concluded that there is a low risk of HBV and HCV infection during gastrointestinal endoscopy.[48] Second, Spach and colleagues published a systematic review 24 years ago in which they identified English-language papers published between 1966 and 1992 about transmission of infection by flexible gastroendoscopy and bronchoscopy. Their results indicated that the most common sources of infection were *Salmonella*, *Pseudomonas*, and *Mycobacterium* species. Nevertheless, those data were based mainly on case reports and were rather outdated.[49]

In contrast, for our systematic review, we used a rigorous process, including sensitive search strategies in five databases and comprehensive selection criteria (no restriction to English-language studies or specific endoscopic examinations), resulting in scientific evidence, judged independently by two reviewers, that could be generalized for all endoscopic examinations. Furthermore, the use of meta-analyses with appropriate subgroup analyses enabled quantification of the associations and led to increased statistical power and precision. Although subgroup differences were not significant, three important trends were observed to contextualize the body of evidence. First, the association between endoscopy and HBV infection was more pronounced when effect measures were adjusted for confounding factors (such as age, sex, and history of blood transfusion). Therefore, appropriate statistical analysis methodology is required to adjust for the effect of confounders to establish a clear link between exposure (i.e., endoscopy) and outcome (i.e., HBV/HCV infection).[50]

Second, the link between endoscopy and HBV/HCV infection tended to be stronger in studies conducted in regions that had higher versus lower HBV/HCV prevalence. Despite this difference, it must be emphasized that the precautionary principle is an important pillar of developing donor-selection criteria. This principle states that, in the interest of public health, risk-management action should be taken even in the absence of certainty about risk, thus aiming for maximum safety.[51] Therefore, the precautionary principle justifies the (temporary) exclusion of donors who have undergone an endoscopic examination, independent of the HBV/HCV prevalence in a specific region (i.e., low risk vs. high risk).

Third, the significant association between endoscopy and HBV infection, as observed in studies conducted before the European Directive (before 2004), could not be demonstrated in studies conducted after the European Directive (2004 and later). However, for HCV, a significant association was observed in both European and non-European studies published both before and after 2004. This suggests that the European Directive, which introduced a deferral period for donors who underwent endoscopy, was not able to break the link between endoscopy and TTIs. Two important factors need to be considered when determining the link between an endoscopic examination and TTIs: the type of decontamination techniques and maintenance of the decontamination system. Effective decontamination will protect the patient from infection, and it can be assumed that decontamination techniques have improved over the past decades. However, our analysis revealed that the association was still present in the studies conducted in the last 10 to 15 years, which may be attributable to maintenance issues. Indeed, several studies reported that the risk of infection due to gastrointestinal endoscopic examination is low when routine procedures are correctly followed[48,52] and that bad maintenance of the decontamination system (e.g., automated endoscope reprocessors) is a common reason for most ready-to-use endoscope contaminations.[53] It would be worthwhile to explore whether the association with TTIs is different when using flexible endoscopes (which have a higher risk of contamination, especially when using manual decontamination methods) compared with rigid endoscopes (which have no contamination risk, because they can be steam sterilized) or to conduct an analysis with stratification based on the decontamination techniques that were used. Unfortunately, none of the studies included here provided information on the type of endoscope or the decontamination techniques, precluding such an analysis.

The major limitation of the current analysis is that we only retrieved data from observational studies in non-blood donor populations (very low quality of evidence). We included two types of observational studies: case-control studies and cohort studies. A case-control study compares individuals who have a specific outcome of interest (i.e., HBV/HCV infection; *cases*) with individuals from the same population source who do not have that outcome (*controls*) to examine the association between the HBV or HCV infection and prior exposure (i.e., endoscopic examination). In our review, we included 26 case-control studies that were not able to provide any data on comparisons before versus after endoscopic HBV or HCV infection, because this is a major limitation of this study type. A cohort study defines a group of individuals (the *cohort*) that is followed over time to examine associations between different interventions (i.e., endoscopic examination) and subsequent outcomes (i.e., HBV or HCV infection). The quality of cohort studies is considered higher than that of case-control studies, because this study type is able to detect new HBV or HCV infections after individuals undergo an endoscopic examination (or not). We included three cohort studies that were not able to show a significant association between HBV or HCV infection and an endoscopic examination.[23,37,42] However, we considered the results of those three studies as imprecise (due to a lack of data,[37] large variation in the results,[23,42] or low numbers of events[37,42]) and the corresponding conclusion as indicating "no evidence of an association" rather than "evidence of an association." To improve the quality of evidence and formulate stronger evidence-based conclusions, well-conducted observational studies (preferably cohort studies) or experimental studies are needed. Only experimental studies (e.g., randomized controlled trials) could clarify whether a direct causal relationship between an endoscopic examination and TTIs is present. Nevertheless, the feasibility and ethics surrounding the set-up of a randomized controlled trial with a control group that receives no intervention is questionable. A potential alternative study design would be a noninferiority study.[54] In

this type of study, a new experimental treatment (e.g., Endoscopic Examination A) will be compared with an active control treatment (e.g., Endoscopic Examination B) to demonstrate that it is not clinically worse with regard to a specified endpoint (e.g., TTIs). In light of the European Directive, a multi-country study in the blood donor population is recommended to increase generalizability of the results.

A second limitation is that the majority of studies (26 of 29 studies) did not use proper criteria (clinical, biochemical, and serological) to distinguish acute from chronic hepatitis infections. For example, the diagnosis of acute hepatitis infection is based on the detection in serum or plasma of HCV/HBV RNA or anti-HCV immunoglobulin G and an elevation of alanine aminotransferase levels. However, none of these markers alone or in combination can be used to identify acute infection, because they may also be detectable during the chronic phase of infection.[54] Differentiating between acute and chronic infection might have an impact on the association with endoscopy, because our subgroup analysis (n = 2 studies; Fig. S1) identified a stronger association (i.e., statistically significant) with patients who had chronic hepatitis. Finally, none of the studies provided detailed information on the type of endoscope that was used.

After the European Directive of 2004 was formulated,[6] blood services in European countries uniformly applied the recommended temporary deferral (i.e., from 4 to 6 months) from blood donation after endoscopic examination. If we want to replace the current precautionary, principle-driven deferral policies by evidence-based deferral policies, we need more high-quality primary research studies to elucidate whether the length of the deferral period (i.e., 4 months for a flexible endoscopic examination procedure), as stated by the European Directive, is still valid.

CONCLUSION

Evidence of very low quality from a systematic review of 29 observational studies revealed that an endoscopic examination is associated with an increased risk of HBV/HCV infection. Further high-quality trials are required to formulate stronger evidence-based recommendations on endoscopic examination as a blood donor deferral criterion.

ACKNOWLEDGMENT

We acknowledge Sandra McElroy (The Language Gap) for checking the grammar and spelling in the article.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Appendix S1. PRISMA checklist.
Appendix S2. Detailed information on the search strategies in the different databases.
Fig. S1. Study-specific ORs representing the association between an endoscopic examination and HBV infection in case-control studies: subgroup analysis (acute vs. chronic HBV infection). Each dot represents the OR of the respective study together with a 95% CI. The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis.
Fig. S2. Study-specific ORs representing the association between an endoscopic examination and HBV infection in case-control studies: subgroup analysis (unadjusted vs. adjusted ORs). Each dot represents the OR of the respective study together with a 95% CI. The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis.
Fig. S3. Study-specific ORs representing the association between an endoscopic examination and HBV infection in case-control studies: subgroup analysis (low-prevalence region vs. high-prevalence region). Each dot represents the OR of the respective study together with a 95% CI. The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis.
Fig. S4. Study-specific ORs representing the association between an endoscopic examination and HBV infection in case-control studies: subgroup analysis (studies published before 2004 vs. studies published in 2004 or later). Each dot represents the OR of the respective study together with a 95% CI. The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis.
Fig. S5. Study-specific ORs representing the association between an endoscopic examination and HBV infection in case-control studies: subgroup analysis (European countries vs. non-European countries). Each dot represents the OR of the respective study together with a 95% CI. The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis.
Fig. S6. Study-specific ORs representing the association between an endoscopic examination and HCV infection in case-control studies: subgroup analysis (acute HCV infection vs. HCV infection). Each dot represents the OR of the respective study together with a 95% CI. The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis.
Fig. S7. Study-specific ORs representing the association between an endoscopic examination and HCV infection in case-control studies: subgroup analysis (unadjusted vs. adjusted ORs). Each dot represents the OR of the respective study together with a 95% CI. The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis.
Fig. S8. Study-specific ORs representing the association between an endoscopic examination and HCV infection in case-control studies: subgroup analysis (low-prevalence region vs. high-prevalence region). Each dot represents the OR of the respective study together with a 95% CI. The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis.
Fig. S9. Study-specific ORs representing the association between an endoscopic examination and HCV infection in case-control studies: subgroup analysis (studies published before 2004 vs. studies published in 2004 or later). Each dot represents the OR of the respective study together with a 95% CI. The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis.
Fig. S10. Study-specific ORs representing the association between an endoscopic examination and HCV infection in case-control studies: subgroup analysis (European countries vs. non-European countries). Each dot represents the OR of the respective study together with a 95% CI. The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis.
Fig. S11. Funnel plot for HBV.
Fig. S12. Funnel plot for HCV.
Table S1. Details of the risk of bias assessment.