Prevalence of Anemia in Inflammatory Bowel Diseases in European Countries: A Systematic Review and Individual Patient Data Meta-analysis

Natalie Filmann, Dipl Math, Julia Rey, Dipl Math,* Sven Schneeweiss, MD,† Sandro Ardizzone, MD,‡ Palle Bager, MPH,§ Gaetano Bergamaschi, MD,‖ Ioannis Koutroubakis, MD,¶ Stefan Lindgren, MD, PhD,** Felipe de la Morena, MD,†† Bjørn Moum, MD,‡‡ Stephan R. Vavricka, MD,§§ Oliver Schröder, MD,† Eva Herrmann, PhD,* and Irina Blumenstein, MD†*

Background: The main objective is to determine the overall prevalence of anemia in inflammatory bowel diseases (IBD) in Europe.

Methods: A systematic literature search in PubMed and Embase was performed for studies published between January 2007 and May 2012. Eligible studies were included if they were original full-paper publications originated from Europe and if the authors agreed to provide their data. An overall prevalence of anemia in IBD, disease specific, and age–gender stratified basis prevalences were estimated. The influence of disease entity (Crohn's disease/ulcerative colitis), gender, age, disease activity (remission/active disease), and IBD-specific treatment strategies on the prevalence of anemia was analyzed by a mixed logistic regression model. Thereby, the factor country of origin was included as a random effect.

Results: Data were available for 2192 patients, mainly treated in tertiary referral centers. The overall prevalence of anemia in IBD patients was 24% (95% confidence interval, 18–31). Age–gender stratified prevalences were estimated for the age strata 18 to 29, 30 to 39, 40 to 49, 50 to 64, 65 to 74, >74 years and ranged from 18% to 35%. Patients receiving IBD-specific medication ($P = 0.0002$, odds ratio 1.54), and patients with active disease status ($P < 0.0001$, odds ratio 2.72) were significantly more likely to have anemia compared with patients not receiving IBD-specific medication or being in remission. Patients with ulcerative colitis tended to have anemia less likely than patients with Crohn's disease ($P = 0.01$, odds ratio 0.77).

Conclusions: The overall prevalence of anemia in patients with Crohn's disease was 27% (95% confidence interval, 19–35) and 21% (95% confidence interval, 15–27) in patients with ulcerative colitis. Thereby, 57% of the anemic patients were iron deficient.

(Inflamm Bowel Dis 2014;0:1–10)

Key Words: anemia, IBD, Crohn's disease, ulcerative colitis, meta-analysis

Anemia represents a common systemic complication in patients with inflammatory bowel disease (IBD). It is a relevant condition affecting quality of life[1,2] and the ability to work.[3]

Two predominant types of anemia have been identified in the context of IBD: iron-deficiency anemia resulting from intestinal bleeding and reduced iron uptake from the enterocyte due to inflammation and ulceration, and the anemia of chronic disease, resulting from inhibition or suppression of erythropoiesis and dysfunction of iron transport.[4] In patients with ulcerative colitis (UC), anemia was identified as influencing the general fatigue score independently of disease activity status.[5]

The reported prevalence of anemia in patients with IBD varies markedly from 6% to 74%, depending on the definition of anemia and on the population considered (e.g., hospitalized patients versus outpatients,[6] Crohn's disease [CD] versus UC, and different treatment strategies). In a systematic review evaluating the prevalence of anemia in patients with IBD in 2008, a mean prevalence of 17% was calculated.[7] However, the prevalence in outpatients was 16% and up to 68% in hospitalized patients.

Assuming that the analysis of a less heterogeneous population will result in more comparable estimates, we determine the overall prevalence of anemia in patients with IBD in

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.ibdjournal.org).

Received for publication December 9, 2013; Accepted December 24, 2013.

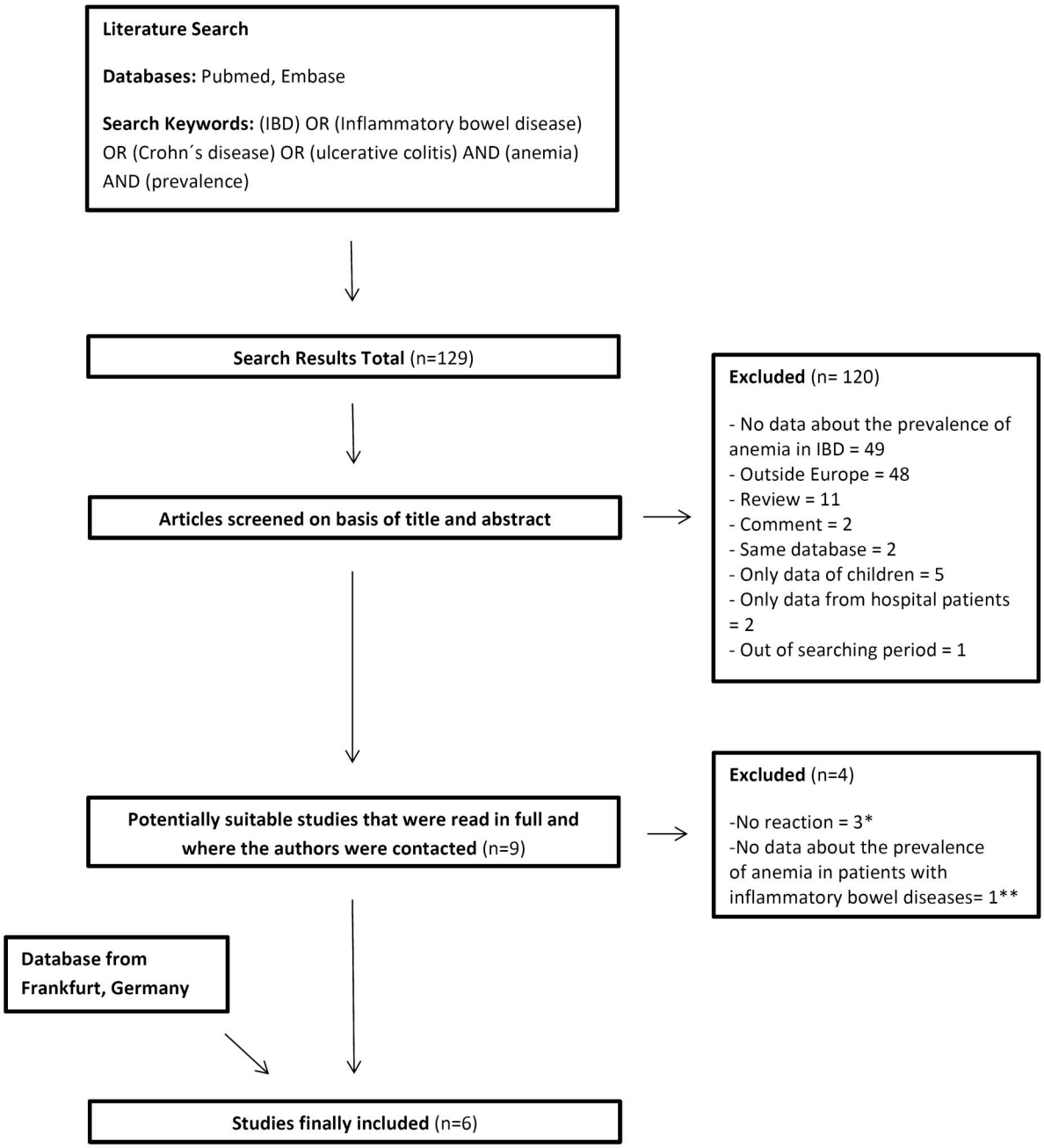
From the *Institute of Biostatistics and Mathematical Modeling, Faculty of Medicine, and †Department of Internal Medicine 1, Goethe-University Hospital, Frankfurt, Germany; ‡IBD Unit, Chair of Gastroenterology, L. Sacco University Hospital, Milan, Italy; §Department of Medicine V (Hepatology and Gastroenterology), Aarhus University Hospital, Aarhus, Denmark; ‖Dip. Area Medica: Medicina Generale 1, Policlinico San Matteo, Pavia, Italy; ¶Department of Gastroenterology, University Hospital Heraklion, Crete, Greece; **Department of Gastroenterology, University Hospital Skane, Malmö, Sweden; ††Sección de Aparato Digestivo, Hospital Infanta Cristina, Parla, Madrid, Spain; ‡‡Department of Gastroenterology, Oslo University Hospital, Oslo, Norway; and §§Division of Gastroenterology, Triemli Hospital, Zurich, Switzerland.

N. Filmann and J. Rey contributed equally to the article.

Reprints: Natalie Filmann, Dipl Math, Goethe-University, Hospital, Theodor-Stern-Kai 7, 60590 Frankfurt, Germany (e-mail: filmann@med.uni-frankfurt.de).

DOI 10.1097/01.MIB.0000442728.74340.fd

Published online.



*Goodhand[24] (124 patients), Rejler[23] (485 patients), Romberg-Camps[5] (707 patients)
**Haapamäki[8] (2831 patients)

FIGURE 1. Flow diagram of study inclusion.

a homogeneous outpatient population treated in specialized mainly tertiary referral centers in Europe. The present meta-analysis is based on individual patient data from recently published literature. Therefore, besides the estimation of the overall prevalence of anemia, it is possible to analyze the influence of several patient characteristics on the prevalence of anemia-like disease entity.

MATERIALS AND METHODS

Literature Search

A systematic literature search in PubMed and Embase was performed independently by 2 researchers (S.S. and I.B.) with the search term "(IBD) OR (Inflammatory bowel disease) OR (Crohn's disease) OR (ulcerative colitis) AND (anemia) AND

TABLE 1. Characteristics of the Studies Evaluating the Prevalence of Anemia

Country	All Data	Denmark	Germany	Greece	Italy	Norway
Study		Bager et al[16]	Blumenstein et al[9,10]	Oustamanolakis et al[17]	Bergamaschi et al[18]	Bager et al[16]
Publication date		2011		2011	2010	2011
n	2192	77	636	100	533	48
Phenotype						
UC	981 (44.75%)	35 (45.45%)	300 (47.17%)	51 (51%)	234 (43.90%)	15 (31.25%)
CD	1210 (55.20%)	42 (54.55%)	336 (52.83%)	48 (48%)	299 (56.10%)	33 (68.75%)
Unclassified	1 (0.05%)			1 (1%)		
Sex						
Female	1039 (47.40%)	40 (51.95%)	338 (53.14%)	42 (42%)	236 (44.28%)	28 (58.33%)
Male	1153 (52.60%)	37 (48.05%)	298 (46.86%)	58 (58%)	297(55.72%)	20 (41.67%)
Average age	43.89	40.1	42.79	49.15	44.74	40.08
Disease activity						
Active	743 (34.16%)	27 (35.06%)	252 (40%)	20 (20%)	202 (37.90%)	27 (56.25%)
Remission	1432 (65.84%)	50 (64.94%)	378 (60%)	80 (80%)	331 (62.10%)	21 (43.75%)
Missing values	17		6			
Hemoglobin average (g/dL)	13.3	13.9	13.5	12.8	12.98	13.1
Median (range)	13.5 (13.6)	14 (7.1)	13.7 (12.800)	12.9 (8)	13 (13.6)	13.3 (6.8)
Anemia[a]	551 (25.14%)	8 (10.39%)	120 (18.87%)	42 (42%)	197 (36.96%)	12 (25%)
Severe anemia (<10 g/dL)	102 (4.65%)	0	26 (4.09%)	8 (8%)	44 (8.26%)	0
Ferritin average (μg/L)	104.77	85.34	NA	67.92	122.3	98.79
Missing values	1174	9			127	
Transferrin saturation (%)	19.6	13.83	NA	18.68	22.42	13.97
Missing values	1281	11			371	1
Anemia of iron deficiency[b]	180/314 (57.32%)	6/77		27/42	95/130 (73.08%)	7/12
Specific IBD medication	1649 (75.26%)[c]	67 (80.19%)	546 (85.85%)	99 (99%)	380 (71.29%)	43 (80.19%)
Remission/active disease	328 (19.89%) 1321	6 (8.96%)/61	68 (12.45%)/478	1/98	50 (13.16%)/330	2/41

Country	Spain	Sweden	Switzerland	*P*
Study	De la Morena and Gisbert[19]	Bager et al[16]	Voegtlin et al[20]	
Publication date	2009	2011	2010	
n	253	304	241	
Phenotype				
UC	117 (46.25%)	125 (41.12%)	104 (43.15%)	NS
CD	136 (53.75%)	179 (58.88%)	137 (56.85%)	
Unclassified				
Sex				
Female	115 (45.45%)	127 (41.78%)	113 (46.89%)	0.0086
Male	138 (54.55%)	177 (58.22%)	128 (53.11%)	

TABLE 1 (*Continued*)

Country	Spain	Sweden	Switzerland	*P*
Average age	46.45	43.36	42.65	0.0001
Disease activity				
Active	28 (11.07%)	125 (41.12%)	62 (26.96%)	0.0001
Remission	225 (88.93%)	179 (58.88%)	168 (73.04%)	
Missing values			11	
Hemoglobin average (g/dL)	13.34	13.6	13.6	0.0001
Median (range)	13.4 (11.8)	13.5 (8.6)	13.9 (10.1)	
Anemia[a]	61 (24.11%)	63 (20.72%)	48 (19.92%)	<0.0001
Severe anemia (<10 g/dL)	9 (3.56%)	4 (1.32%)	11 (4.56%)	<0.0001
Ferritin average (μg/L)	108.83	97.08	NA	
Missing values	149	12		
Transferrin saturation (%)	25.73	15.97	NA	
Missing values	1	20		
Anemia of iron deficiency[b]	2/61 (3.28%)	43/61 (70.49%)		
Specific IBD medication	98 (38.74%)[d]	234 (76.97%)	126 (52.5%)*	<0.0001
Remission/active disease	71 (72.45%)/27	49 (20.94%)/185	82 (65.08%)/44	

NA, not available; n.s., not significant.

[a]Defined as hemoglobin levels of <13 g/dL in men and <12 g/dL in women.

[b]Anemia of iron deficiency was defined as Transferrin saturation below 16 % or serum Ferritin below 30 μg/L (patients in remission), respectively below 100 μg/L (patients during active disease).

[c]One missing value.

[d]Regarding the Spanish cohort only the use of corticosteroids was recorded. No information is available about different IBD-specific medication that was given.

(prevalence)." The search included studies from January 2007 until May 2012. In addition, reference lists of studies fulfilling the inclusion criteria were inspected.

Studies were included in the meta-analysis if they were original full-paper publications from Europe that evaluated the prevalence of anemia in patients with IBD. Authors from fully published articles were contacted per e-mail and were asked to contribute the following data for each patient:

Disease entity (CD/UC), gender, age, country of origin, Crohn's disease activity index, Harvey–Bradshaw index, Colitis activity index, simple clinical colitis activity index, disease activity (remission/active disease), hemoglobin, ferritin, transferrin saturation, information about IBD-specific medication, corticosteroids (including budesonide), 5-aminosalicylic acid (5-ASA), immunosuppressive medication, and biologics.

Studies were excluded if they were reviews, letters to the editor, or abstracts. Furthermore, studies were excluded if data from countries outside Europe, data of children, or of in-hospital patients were reported or if patient data does not include any laboratory tests showing anaemia.[8] Details are given in Figure 1.

In addition, we analyzed a German data set (n = 636) that has been published in a different context[9,10] (see Appendix, Supplemental Digital Content 1, http://links.lww.com/IBD/A409, for more detailed information concerning these data).

Statistical Methods

We considered anemia as a binary outcome variable (yes/no). Therefore, we used the definition of the World Health Organization, in which existence of anemia is defined as hemoglobin levels of <13 g/dL in men and <12 g/dL in women.[11]

An overall prevalence of anemia and of severe anemia of all included European countries with the corresponding 95% confidence interval (CI) was estimated by the random-effects model (DerSimonian and Laird estimator)[12] using the Freeman–Tukey double arcsine-transformation.[13,14] The proportions of the single studies were calculated from the individual patient data. The random-effects model accounts for heterogeneity of the different studies in the analysis of the overall prevalence. Studies with larger sample size and therefore a smaller standard error received more weight when calculating the mean prevalence.

Furthermore, an overall prevalence was separately estimated for patients with CD and UC by the random-effects model. Factors (i.e., disease entity [CD/UC], gender, age, and disease activity) (remission/active disease) and the influence of treatment (IBD-specific medication) that may influence the development of anemia (yes/no) were analyzed by a logistic regression model with mixed effects fitted with a maximum likelihood approach. In addition, the difference in transferrin saturation in anemic and nonanemic patients was examined by a mixed linear regression model.

All analyses were performed using R software (package lme4 by D. Bates, M. Maechler, and B. Bolker (0.999999–0, June 23, 2012), package meta by G. Schwarzer (2.1–4, November 29, 2012), version 2.14; the R Foundation for Statistical Computing, Vienna, Austria).

Mixed effect models are suitable for analyzing longitudinal or clustered data because they take correlations into account that arise from dependent data.[15] In our data set patients are clustered into different countries. Because we were interested in analyzing the prevalence of anemia in patients with IBD in Europe, we considered the countries included in the meta-analysis as a random

TABLE 2. Quality Assessment of the Evaluated Studies

Study	Germany[a]	Greece	Italy	Scandinavia	Spain	Switzerland
	Blumenstein et al[9,10]	Oustamanolakis et al[17]	Bergamaschi et al[18]	Bager et al[16]	De la Morena and Gisbert[19]	Voegtlin et al[20]
Study Design						
Setting	NA	Yes[a]	Yes	Yes	Yes	Yes
Selection of patients	NA	Yes	Yes	Yes	Yes	Yes
Study size	NA	Yes	Yes	Yes	Yes	Yes
Bias	NA	Yes[b]	Unclear	No	Unclear	Yes
Results						
Characteristics of patients	NA	Yes	Yes	Yes	Yes	Yes
Missing data	NA	No missing values	No	Yes[b]	Yes	Yes
Discussion						
Limitations	NA	Yes	No	Yes	Yes[b]	Yes

Setting—is information about study design, type of study, relevant dates, periods of recruitment, data collection given? Selection of patients—are inclusion and exclusion criteria described? Study size—is the study size explained in detail? Bias—description of any efforts to address potential sources of bias? Characteristics of patients—are numbers of individuals reported at each stage of study? Missing data—are missing values reported; are limitations of the study discussed?

[a]Period of recruitment is missing.

[b]Yes/no/unclear: clarified by the examination of the individual patient data and by the authors of the studies.

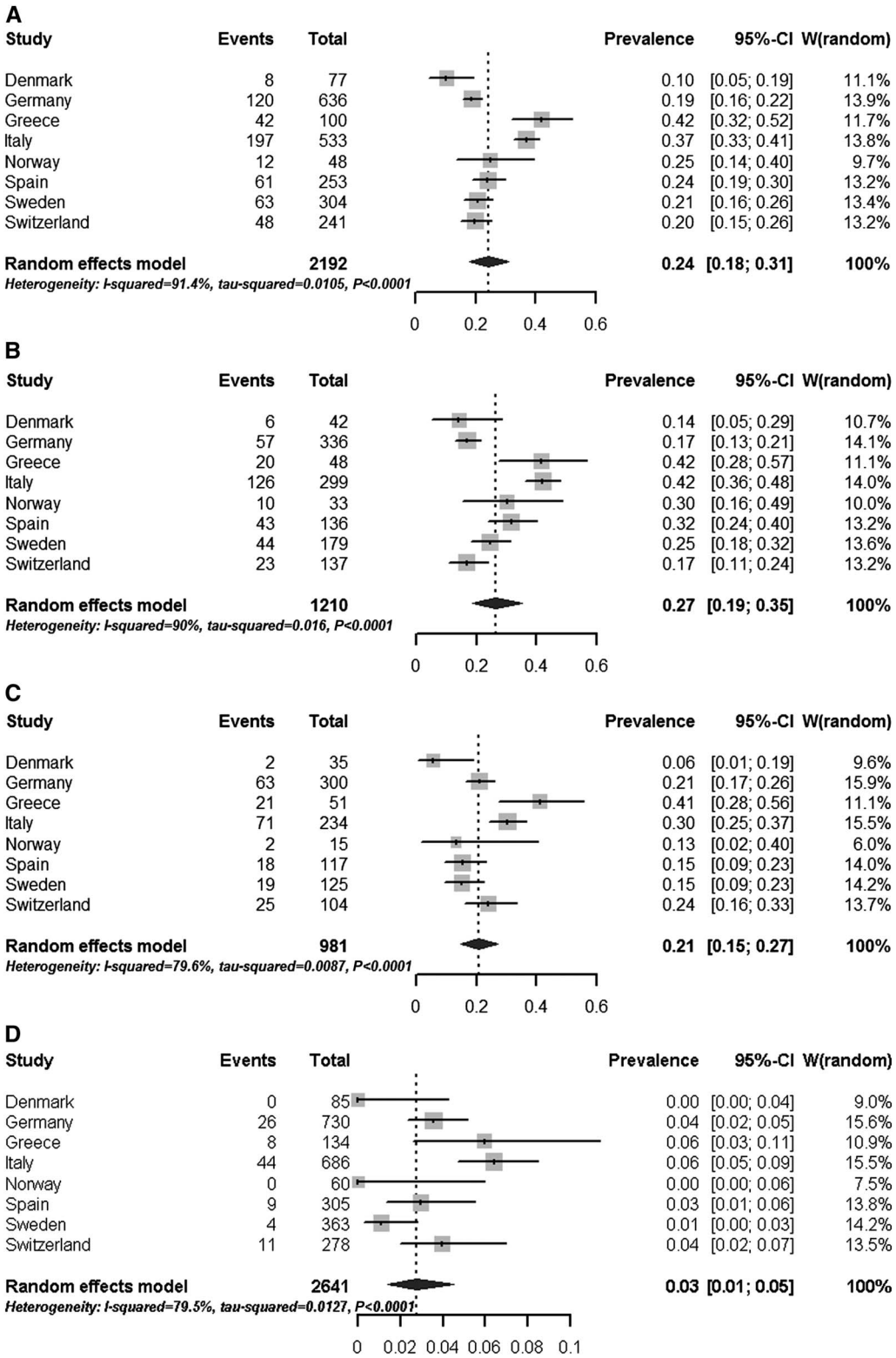


FIGURE 2. Forest plot from meta-analysis of the prevalence of anemia in IBD patients. Forest plots for all patients (A), for patients with CD (B), for patients with UC (C), and of the prevalence of severe anemia (all patients) (D) by the random-effects model. The size of the squares is shown proportional to the weight that the respective study contributes to the estimator of the overall prevalence. Studies with a larger sample size get more weight than studies with a small sample size.

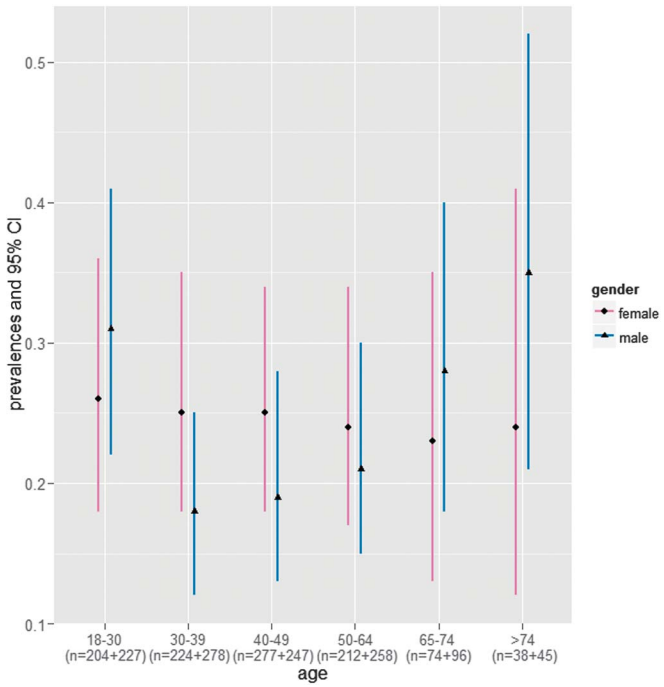


FIGURE 3. Basis prevalences of anemia for the different age groups basis prevalences with 95% CI for the different age groups classified by gender, n consists of the number of female patients plus the number of male patients for each age group.

sample of all European countries. Hence the factor "country of origin" was included as a random effect.

Regarding patients characteristics in Table 1, the Kruskal–Wallis test was used to compare continuous variables between groups and the chi-square test was used to compare categorical variables (BiAS, version 10.02, epsilon-Verlag; Hochheim, Darmstadt, Germany). All tests were 2-tailed and a P value of less than 0.05 was considered significant.

The quality of the included studies was assessed by selected items from the STROBE statement.[21] If the documentation in the published studies was insufficient, the authors of the corresponding studies were contacted to provide the missing information if possible. The meta-analysis was performed according to the guideline Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA Statement).[22]

RESULTS

The literature search yielded 129 studies for the search period evaluating the prevalence of anemia. Finally, 9 studies fulfilled the inclusion and exclusion criteria. Together with the German data set individual patient data could be obtained from 6 studies, which were performed in Germany, Greece, Italy, Scandinavia (Denmark, Norway, and Sweden), Switzerland, and Spain.[16–20] The German data set was published in a different context.[9,10] A sensitivity analysis was performed to assess whether results change if the German data set is excluded (not shown). Data were available for 2192 patients, but the data sets were heterogeneous. Because data sets were recorded for studies with distinct aims, we could not distinguish between patients with anemia of chronic disease, iron-deficiency anemia, or a combination of both. Details are shown in Figure 1. The 6 studies present various patient characteristics that are described in Table 1. The quality of the studies was rated by a checklist based on the STROBE statement.[21] Items were rated as "yes," "no," or "unclear." The results are summarized in Table 2.

Overall and Age–Gender Stratified Prevalence of Anemia

The overall prevalence of anemia in all IBD patients was given by 24% (95% CI, 18–31) and the overall prevalence of severe anemia by 2.75% (95% CI, 1.4–4.5). Patients with CD showed an overall prevalence of 27% (95 CI, 19–35) and patients with UC overall prevalence of 21% (95% CI, 15–27). Age–gender stratified basis prevalences were estimated for the age strata 18 to 29 years (male: 31% [95% CI, 22–41], female: 26%, [95% CI, 18–36]), 30 to 39 years (male: 18% [95% CI, 12–25], female: 25% [95% CI, 18–35]), 40 to 49 years (male: 19% [95% CI, 13–28], female: 25% [95% CI, 18–34]), 50 to 64 years (male: 21% [95% CI, 15–29], female: 24% [95% CI, 17–33]), 65 to 74 years (male: 28% [95% CI, 18–40], female: 23% [95% CI, 13–35]), and >74 years (male: 35% [95% CI, 21–52], female: 24% [95% CI, 12–41]). Detailed results are presented in Figures 2 and 3.

Factors Associated with the Existence of Anemia

Univariate logistic regression with mixed effects revealed that patients with active disease status ($P < 0.0001$, odds ratio [OR] 2.72) were significantly more likely to have anemia than patients being in remission. Patients with UC inclined to have less likely anemia than patients with CD ($P = 0.011$, OR 0.77). Gender was not significantly associated with the existence of anemia. In addition, we revealed that male patients between 31 and 64 years have a significantly lower risk for anemia than patients between 18 and 30 years (age strata 31–39 yr: OR 0.50, $P = 0.001$, 40–49 yr: OR 0.56, $P = 0.008$, 50–64 yr: 0.63, $P = 0.026$), for IBD patients older than 65 years and female patients, we found no significant association between age and anemia.

To test whether IBD-specific medication was correlated with anemia, we stratified the data set by disease status. It turned out that patients in remission receiving IBD-specific medication (OR 1.40, $P = 0.039$) and having CD (OR 0.77, $P = 0.007$) have a significantly higher prevalence of anemia than patients receiving no IBD-specific medication and having UC, respectively. We found a significant association and a trend between age and anemia in male patients (reference group: 18–30 yr, age strata 31–39 yr: OR 0.38, $P = 0.001$, age strata 40–49 yr: OR 0.58, $P = 0.059$, age strata 50–64, 65–74, >74 yr: nonsignificant), but not for female patients. Gender was not associated with anemia.

For patients with active disease, we did not find any significant associations for the factors IBD-specific medication, disease entity, age, or gender. The results of the univariate logistic regression analysis with mixed effects are shown in Table 3.

TABLE 3. Univariate Logistic Regression Analyses with Mixed Effects

	All patients		Subgroup Remission		Subgroup active disease	
Univariate Analysis	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
IBD-specific medication: no IBD-specific medication	—[a]	—	1.40 (1.02-1.92)	0.039	—	NS
Disease entity—UC: CD	0.77 (0.62–0.96)	0.011	0.69 (0.53–0.91)	0.007	—	NS
Active disease: remission	2.72 (2.19–3.37)	<0.0001	—	—	—	—
Age (yr)						
(Male) 18–29	Reference group	—	Reference group	—	Reference group	—
30–39	0.50 (0.35–0.72)	0.001	0.38 (0.21–0.69)	0.001	—	NS
40–49	0.56 (0.37–0.85)	0.008	0.58 (0.33–1.02)	0.059	—	NS
50–64	0.63 (0.41–0.96)	0.026	—	NS	—	NS
65–74	—	NS	—	NS	—	NS
>74	—	NS	—	NS	—	NS
Age (yr)						
(Female) 18–29	—	NS	Reference group	—	Reference group	—
30–39	—	NS	—	NS	—	NS
40–49	—	NS	—	NS	—	NS
50–64	—	NS	—	NS	—	NS
65–74	—	NS	—	NS	—	NS
>74	—	NS	—	NS	—	NS
Gender—female:male	—	NS	—	NS	—	NS

NS, nonsignificant.
[a]Test here only useful for subgroups remission and active disease.

Transferrin Saturation and Ferritin Values

Transferrin saturation varied significantly between anemic and nonanemic patients (mean 12.44% versus 15.63%, $P = 0.008$). For anemic patients where transferrin saturation or ferritin values were available, we analyzed whether anemia was caused by iron deficiency: In total, 180 of 314 anemic patients (57.32%) had transferrin saturation below 16% or serum ferritin below 30 μg/L (patients in remission), respectively, below 100 μg/L (patients during active disease) (Table 1).

Prevalences of Studies Not Included in Our Meta-analysis from 2000 to 2012

In Table 4, the prevalences of all relevant studies not included in our meta-analysis from 2000 until May 2012 are summarized. Reported prevalences ranged from 3.2% to 48%. A possible time effect (2000–2012) is analyzed by a weighted linear regression ($P > 0.1$). The prevalences of all studies between 2000 and 2012 included and not included in our meta-analysis are illustrated by a bubble plot (Figure 4).

DISCUSSION

Anemia is common in IBD patients and should be investigated with care as it can be caused by several factors.[28,29] Although treatment of anemia results in significant improvement of the health-related quality of life and is the most frequent comorbid condition in IBD patients, its necessity had been underestimated for a long time.[28,29] Data on the prevalence of anemia in patients with IBD ranges enormously from 6% to 74% with the highest prevalence in older studies and for hospitalized patients.[6,30]

In 2007, guidelines for the screening and the treatment of anemia in patients with IBD were introduced by a group of European IBD specialists.[28] This meta-analysis summarizes the prevalence of anemia in European countries for the period of January 2007 to May 2012.

The systematic literature search revealed individual patient data from 8 different countries evaluating the prevalence of anemia in IBD. According to our checklist of selected items of the STROBE statement,[21] the 5 studies were of good quality. The overall prevalence of anemia in patients with IBD of the included European countries was given by 24% and an iron deficiency in about 57% of the anemic patients. Prevalence of anemia in patients with IBD was quite comparable in Germany, Norway, Spain, Sweden, and Switzerland (range, 18%–25%). One reason for this observation might be the rather homogeneous data from these studies because all patients were mainly treated in tertiary centers, and were not hospitalized in most cases (only the Swiss data set includes 116/241 inpatients). We suppose that the implementation of the 2007 guidelines may be another reason for the homogeneous prevalence as prevalence in outpatients from studies published between 2000 and 2006 range between 6% and 60%,[6] but there is no direct comparison available.

TABLE 4. Overview of Studies Not Included in the Present Meta-analysis (January 2000–May 2012)

Study	Country	Publication Date	Hospitalization	n	Phenotype	Prevalence of Anemia (%)	Definition of Anemia (g/dL)
Rejler et al[23,a]	Sweden	2012	Outpatient	485	IBD	6	M: Hb <13; F: Hb <12
					CD	9	
					UC	5	
Goodhand et al[24,a]	United Kingdom	2011	Outpatient	124	IBD	40	M: Hb <13; F: Hb <12
					CD	48	
					UC	45	
Romberg-Camps et al[5,a]	The Netherlands	2010	Outpatient and hospitalized	707	IBD	9.2	M: Hb <13.69; F: Hb <12.08
					CD	11.5	
					UC	7.3	
Vijverman et al[25]	Belgium	2006	Outpatient	90	IBD	16.7 (2003)	M: Hb <13; F: Hb <11.6
Ebinger et al[26]	Germany	2004	Outpatient	599	IBD	4.8	NA
					CD	3.2	
					UC	6.2	
Lakatos et al[27]	Hungary	2003	Outpatient	254	IBD	26.5	NA
					CD	35.8	
					UC	25	

[a]Authors were contacted but did not respond or the required data were not available.

Individual data meta-analyses are considered as the highest level method for summarizing the results of multiple studies. The availability of this large database facilitates to adjust for the heterogeneity at the patient level: it allows us to gain more reliable estimates for risk factors and for the prevalence of anemia in patients with IBD in Europe for different strata as disease activity status. Furthermore, a homogeneous definition of anemia and iron deficiency according to the 2007 and the ECCO guidelines could be used.[28,31]

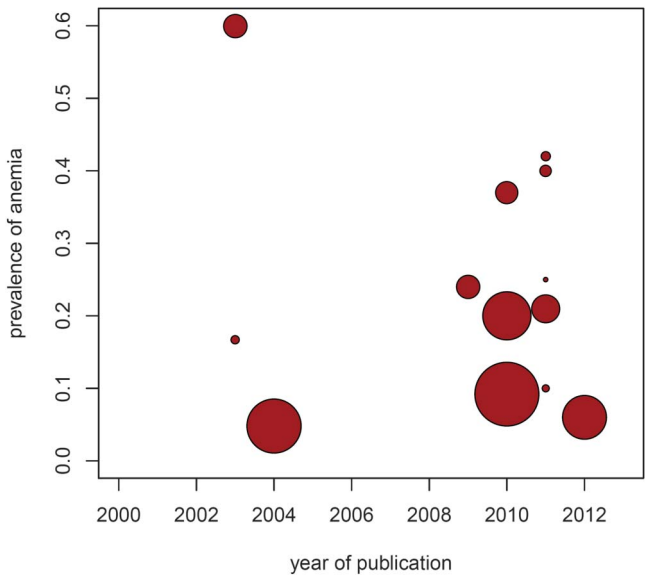


FIGURE 4. Bubble plot on the prevalence of anemia for all studies published between January 2000 and May 2012. A bubble plot shows the influence of the date of publication on the prevalence of anemia for all studies published between January 2000 and May 2012 included and not included in the meta-analysis. The size of the bubbles is chosen according to the sample size of the individual studies.

It can be anticipated that the heterogeneity of public health care systems in Europe with respect to the choice of IBD-specific treatment and treatment of anemia contributes to the heterogeneity in the prevalence of anemia. Especially, the high prevalences of anemia in Greece (42%) and Italy (37%) may be explained by the differing health care systems but the heterogeneity of the data sets with respect to other factors has to be considered as well. It is of notice that both Greece and Italy had also the higher prevalence of severe anemia (8% and 8.26%, respectively). In further current European studies not included in the present analysis, the prevalences of anemia in IBD patients ranged from 7% in Sweden,[23] to 9% in the Netherlands,[5] and to 40% in the United Kingdom.[24]

The systematic review of Kulnigg and Gasche in 2006[6] included 19 studies from European countries, the United States, Israel, and Australia. The publication years of the individual studies dated from 1968 to 2006 and included inpatients and outpatients. In contrast to our present meta-analysis, the included studies show very diverging prevalence of anemia in IBD patients, which ranged from 6% in a German study (published in 2004, outpatients) to 74% in a U.S. study based on inpatients, published in 1977.

The prevalence of anemia was significantly higher in patients with CD (27%) than in patients with UC (21%). Besides chronic intestinal blood loss through ulcerated mucosal surface,

which occurs in both disease entities, patients with CD in the upper gastrointestinal regions have an additional risk of iron malabsorption leading to iron deficiency anemia, possibly explaining this difference.[6]

Furthermore, an age–gender stratified basis prevalence was estimated and showed that male patients between 30 and 64 years seem to have a significantly lower risk for anemia than younger patients (<30 yr) or men older than 65 years; whereas for women, the prevalence is almost equal in every stage of life (a possible explanation for the difference would be the blood loss during menstruation in young females).

A univariate analysis of the factors age, gender, disease status, and entity revealed that CD (compared with UC) and an active disease status were significantly associated with the existence of anemia. After stratifying for disease activity status, it turned out that patients being in remission treated with IBD-specific medication or CD have a significantly higher prevalence of anemia.

A detailed analysis of the influence of different IBD-specific treatment strategies on anemia was not in the scope of the present meta-analysis because information about dosage, treatment duration, and the duration of remission of the included patients were missing, and the observational studies do not include randomized treatment arms. However, we could distinguish whether patients receive IBD-specific medication for the treatment of active disease or for preventing active disease while being in remission. Thus, possible associations between the prevalence of anemia and the different medication of IBD may be explained by the severity of disease and need to be evaluated in randomized clinical trials.

Nevertheless, for patients with active disease, we did not find any significant association in IBD-specific medication, disease entity, age, or gender despite the comparably high sample size.

In summary, the present meta-analysis with individual patient data from 6 studies with overall 2192 patients revealed a homogeneous prevalence of anemia of around 24% patients with IBD in Europe.

REFERENCES

1. Pizzi LT, Weston CM, Goldfarb NI, et al. Impact of chronic conditions on quality of life in patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2006;12:47–52.
2. Wells CW, Lewis S, Barton JR, et al. Effects of changes in hemoglobin level on quality of life and cognitive function in inflammatory bowel disease patients. *Inflamm Bowel Dis.* 2006;12:123–130.
3. Cucino C, Sonnenberg A. Cause of death in patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2001;7:250–255.
4. Gasche C, Lomer MCE, Cavill I, et al. Iron, anaemia and inflammatory diseases. *Gut*. 2004;53:1190–1197.
5. Romberg-Camps MJL, Bol Y, Dagnelie PC, et al. Fatigue and health-related quality of life in inflammatory bowel disease: results from a population-based study in the Netherlands: the IBD-South Limburg Cohort. *Inflamm Bowel Dis.* 2010;16:2137–2147.
6. Kulnigg S, Gasche C. Systematic review: managing anemia in Crohn's disease. *Aliment Pharmacol Ther.* 2006;24:1507–1523.
7. Gisbert JP, Gomollón F. Anemia and inflammatory bowel diseases. *World J Gastroenterol.* 2009;15:4659–4665.
8. Haapamäki J, Roine RP, Turunen U, et al. Increased risk for coronary heart disease, asthma, and connective tissue diseases in inflammatory bowel disease. *J Crohns Colitis.* 2011;5:41–47.
9. Blumenstein I, Bock H, Weber C, et al. Health care and cost of medication for inflammatory bowel disease in the Rhein-Main region, Germany: a multicenter, prospective, internet-based study. *Inflamm Bowel Dis.* 2008;14:53–60.
10. Blumenstein I, Herrmann E, Filmann N, et al. Female patients suffering from inflammatory bowel diseases are treated less frequently with immunosuppressive medication and have a higher disease activity: a subgroup analysis of a large multi-centre, prospective, internet-based study. *J Crohns Colitis.* 2011;5:203–210. doi:10.1016/j.crohns.2010.12.012.
11. World Health Organization. *Iron Deficiency Anaemia: Assessment, Prevention, and Control. A Guide for Programme Managers*. Geneva, Switzerland: World Health Organization; 2001. (WHO/NHD/01.3).
12. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7:177–188.
13. Freeman MF, Tukey JW. Transformations related to the angular and the square root. *Ann Math Stat.* 1950;21:607–611.
14. Miller JJ. The inverse of the Freeman-Tukey double arcsine transformation. *Am Stat.* 1978;32:138.
15. Pinheiro JC, Bates DM. *Mixed-effects Models in S and S-Plus*. New York, NY: Statistics and Computing Series, Springer; 2009.
16. Bager P, Befrits R, Wikman O, et al. The prevalence of anemia and iron deficiency in IBD outpatients in Scandinavia. *Scand J Gastroenterol.* 2011;46:304–309.
17. Oustamanolakis P, Koutroubakis IE, Messaritakis I, et al. Measurement of reticulocyte and red blood cell indices in the evaluation of anemia in inflammatory bowel disease. *J Crohns Colitis.* 2011;5:295–300.
18. Bergamaschi G, Di Sabatino A, Albertini R, et al. Prevalence and pathogenesis of anemia in inflammatory bowel disease. Influence of anti-tumor necrosis factor-alpha treatment. *Haematologica*. 2010;95:199–205.
19. De la Morena LP, Gisbert JP. Prevalence and characteristics of anemia in inflammatory bowel diseases. *Gastroenterol Hepatol.* 2009;32:391–399.
20. Voegtlin M, Vavricka SR, Schoepfer AM, et al. Prevalence of anaemia in inflammatory bowel disease in Switzerland: a cross-sectional study in patients from practices and university hospitals. *J Crohns Colitis.* 2010;4:642–648.
21. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Bull World Health Organ.* 2007;85:867–872.
22. Liberati A, Altman DG, Tetzlaff J, et al The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62:e1–e34.
23. Rejler M, Tholstrup J, Andersson-Gäre B, et al. Low prevalence of anemia in inflammatory bowel disease: a population-based study in Sweden. *Scand J Gastroenterol.* 2012;47:937–942.
24. Goodhand JR, Kamperidis N, Rao A, et al. Prevalence and management of anemia in children, adolescents, and adults with inflammatory bowel disease. *Inflamm Bowel Dis.* 2012;18:513–519.
25. Vijverman A, Piront P, Belaiche J, et al. Evolution of the prevalence and characteristics of anemia in inflammatory bowel diseases between 1993 and 2003. *Acta Gastroenterol Belg.* 2006;69:1–4.
26. Ebinger M, Leidl R, Thomas S, et al. Cost of outpatients with inflammatory bowel disease in a German University Hospital. *J Gastroenterol Hepatol.* 2004;19:192–199.
27. Lakatos L, Pandur T, David G, et al. Association of extraintestinal manifestations of inflammatory bowel disease in a province of western Hungary with disease phenotype: result of a 25-year follow-up-study. *World J Gastroenterol.* 2003;9:2300–2307.
28. Gasche C, Berstad A, Befrits R, et al. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. *Inflamm Bowel Dis.* 2007;13:1545–1553.
29. Gisbert JP, Gomollón F. Common misconceptions in the diagnosis and management of anemia in inflammatory bowel disease. *Am J Gastroentrol.* 2008;103:1299–1307.
30. Wilson A, Reyes E, Ofman J. Prevalence and outcomes of anemia in inflammatory bowel disease: a systematic review of the literature. *Am J Med.* 2004;116(suppl 7A):44S–49S.
31. Van Assche G, Dignass A, Bokemeyer B, et al. European Crohn's and Colitis Organisation. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 3: special situations. *J Crohns Colitis.* 2013;7:1–33.