Review

The Prevalence of Shiga Toxin-producing Escherichia Coli in Patients with Gastroenteritis in Iran, Systematic Review and Meta-analysis

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Shiga toxin induced Escherichia Coli (STEC) is associated with chronic kidney disease or neurologic disability. The aim of this study is to determine the prevalence of STEC identified in human studies in Iran. Search engines of PubMed, EMBASE, OVID, SCOPUS, Web of Science, Google Scholar, IranMedex, MagIran, SID and ganj.irandoc were used. All human studies with stool or rectal swap samples evaluated for STEC and the outcome of HUS in Iran, which had been published between 1985 and 2017, were included. Chi-square and I2 statistic tests were applied to assess between-studies heterogeneity. Pooled prevalence and odd ratio were calculated using random effect models. A total of 30 articles containing 23379 samples were included for the final analysis. The design of study was cross sectional in 16, case control in 13 and one was cohort. The pooled prevalence of STEC was 7% (95% CI, 5 – 11; I^2 = 98.3%). In subgroup analysis, the pooled prevalence was 8% (95% CI, 4 – 13; I^2 = 97.55%) in children but 4% (95% CI, 2 – 7; I^2 = 97.66%) in adults. The odds of patients with diarrhea having had STEC were 7.06 times the odds of healthy subjects (pooled OR = 7.06, 95% CI: 3.66-13.61). Patients with bloody diarrhea less likely to have positive STEC than patients with non-bloody diarrhea (pooled OR = 0.33, 95% CI: 0.10-1.02). STEC was prevalent in diarrheic patients and the rate increased in recent years. The highest contamination was seen in East-South of Iran. Public health intervention is mandatory to eliminate it effectively.

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INTRODUCTION

Shiga toxin induced Escherichia Coli (STEC) is responsible for diarrhea associated hemolytic uremic syndrome (HUS). The infection is associated with morbidity and mortality. STEC is the most common cause of post-infectious HUS with annual estimation of 3890 cases.[1] Subsequent to adherence of STEC to intestinal epithelium, Shiga toxins (Stx), having a very short serum half-life and a high affinity to bind to microvasculature, bind to G3b receptors and pass through intestinal barrier. Through blunting the cytokine response, STEC withstand the intestinal eviction.[2]

To facilitate detection of atypical STEC, some laboratories expanded the capabilities to identify the contaminated cases.[3] There is a tendency of antibiotic prescription for bloody diarrhea by physicians. Antibiotic usage in patients contaminated with STEC might increase the risk of HUS [OR: 2.24 (95% CI: 1.45 - 3.46)].[4]

STEC and D + HUS are not enlisted in contagious disease catalogue offered by Ministry of Health

and Medical Education in Iran.[5] Therefore, in the absence of surveillance of STEC, many infected cases are not recognized. The purposes of this systematic review were to detect the prevalence and incidence of confirmed Shiga toxin-producing E. coli (STEC) in subjects with gastroenteritis and to depict the outcome.

MATERIALS AND METHODS

Protocols and Registration

The study was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA statements).[6] The protocol for this systematic review was registered on PROSPERO (CRD42016033019) and is available in full on the http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID = CRD42016033019.[7]

Search Strategy

Systematic search was performed by two independent reviewers (N, H and A, A) in several international and national databases including PubMed, Google Scholar, OVID, SCOPUS, Web of Sciences, MagIran, health.barakatkns.com, SID.ir, dociran, PDFiran, Ganj.irandoc, and abstract books of congresses from 1985 to August 2018. The PICO of systematic review and meta-analysis used to find the relevant studies. The search strategy was made using the "Mesh" subject heading and free text word like, ("Diarrhea"[Mesh]) OR "Gastroenteritis"[Mesh]) AND ("shigatoxin" or "enterohaemorrhagic e coli" or "escherichia coli o157" or "escherichia" or "escherichia coli o157" or "enterohemorrhagic escherichia coli") AND ("haemolytic uraemic syndrome" or " hemolytic-uremic syndrome") AND ("shiga toxins" or "verocytotoxin " or " toxins"). Besides, we checked bibliography of included articles for further references. We made contact through email by authors if the data was missed in the report. There was no limitation of age and all studies with Persian and English language were included in this study. We narrowed the search by limiting the survey to Iran and publication period between 1985 and 2018. The search re-runs just before the final analyses and if relevant studies are found they were included.

Study Selection

We used the following inclusion and exclusion criteria to include the relevant articles in this meta-analysis. We include all observational studies (cohort, case-control, cross-sectional) if they meet the eligibility criteria. Patients presented with gastroenteritis, diarrhea, hemorrhagic colitis, dysentery, or hemolytic uremic syndrome that investigated for STEC infection were included. There was no limitation of age and language. The settings were hospitals, outpatient facilities, day-care centers, and military institutions. STEC infection identified by using Sorbitol-MacConkey (SMAC) agar, followed by sero-typing by any of the recognized techniques such as latex, slide, or tube agglutination test, and/or confirmed by PCR for rfbO157 or other STEC-specific genes. Two independent reviewers (AA, SN) screening the studies by title, abstract, full text and, in the case of discrepancy "NH" was arbiter.

Quality Assessment

STROBE statement was used to assess the quality of studies which includes 12 questions that cover different methodological aspects such as sample type, determining the appropriate sample size, sampling method, study population, the data collection method, definition of variables and method of examining the samples, data collection tools, statistical analysis, purpose of the study, appropriate way of reporting findings and reporting findings based on objectives.[8] If the studies get more than 80 percent of total score consider as high quality, 60-79% of total score as intermediate quality and 30-59% of total score they classified as low quality.[8,9] N, H and A, A independently was investigating the quality of each included study.

Data Extraction

Two of the authors (S, N and A, A) independently extracted data from studies using a pre-specified sheet in Microsoft Excel 2010 as follows: Bibliography; Language, center, type, and period of study, sample size, patient information (age, disease, gender), technique of culture, using serology study, and of STEC detection, type of STEC (1, 2, both), method of bacterial genum extraction, type of E.Coli, length of follow up, outcome- recovery, HUS, death, unreported, funding sources. Disagreement was resolved by discussion between the two reviewers and if required, senior investigator (N, H) solved the discrepancies.

Table 1. A Summary of The Articles About The Shiga Toxin Escherchia Coli (STEC) in Human

StudyID	Study Design	Age	symptoms	Gender	Date of study city	Total (N)	Type of Sample	Positive for STEC (n)	Identifying method	STORBE /BIAS
Mehrabiyan S,2012 (23)	CS	Children+ adult	diarrhea	F:35, M:28	2011	110	fecal	5	PCR	Good/fair Low
Aslani MM,2009 (24)	CC	adult	Diarrhea Healthy	F:19, M:10	1997-1999 Ilam Mazandaran	5276	fecal	29 (D- 6, H-23) Stx1-28 Stx2-1 hlyA-13	PCR	Good/fair Low
Bonyadian M,2010 (25)	CS	children	diarrhea	F:111, M:89	2007-2008 Shahrekord	200	fecal	28 Stx1-16 Stx2- 4 Stx1,2- 8 No HUS	PCR	Good/fair Low
Kargar M,2014 (26)	CS	children <5 yr	Diarrhea Mild D-52 Severe D-51 Vomiting-73 Fever-64	F:138, M:162	2011-2012 Yasuj	300	fecal	104 Stx1-14 Stx2-31 Stx1,2-9 eaeA-stx1-12 eaeA-stx2-25 eaeA-stx1,2- 13	PCR	Good/fair Low
Aslani MM,2008 (27)	CC	UA	diarrhea	UA	2005 Pasteur Institute	193	fecal	86 stx	PCR	Good/fair Low
Nahaie MR,2007 (14)	C	children	diarrhea	UA	2003-2006	1020	fecal	Ecoli O157-6 Stx- UA	SAT	Good/fair Low
Akbari A,2009 (28)	CS	children	diarrhea	UA	2008	300	fecal	9 Stx1/2-9	PCR	Good/fair Low
Naeb-Agaie SM,2006 (29)	CS	UA	diarrhea	UA	1999-2000	500 E.coli	Feces-189, urine-311	Feces-2 Urine -1 VT2-3	PCR	Good/fair Low
Aslani MM,2007 (30)	CC	children	Diarrhea Hemorrhagic colitis	F:63, M:77	2004	140	fecal	14 Stx O142:H48-2 O111:H23-1 O26:H4-2 O126:H47-1 O126:H6-1	PCR-RFLP	Good/fair Low
Alikhani MY,2007 (31)	CC	children 6m-10 yr	Diarrhea Control	F:612, M:680	2003	1292	fecal	39	SAT	Good/fair Low
Alborzi A,2008 (32)	CS	Children 2m-14 yr	diarrhea	UA	2003	719	fecal	0	PCR	Good/fair Low
Momtaz H, 2013 (33)	CC	Children <60 m	Diarrhea Non-diarrhea	UA	2012-2013	308	fecal	122 stx	PCR	Good/fair Low

Table 1. Continued

StudyID	Study Design	Age	symptoms	Gender	Date of study city	Total (N)	Type of Sample	Positive for STEC (n)	Identifying method	STORBE /BIAS	
Haghi F,2014 (34)	CC	children	diarrhea	F:236, M:364	2011-2012	600	fecal	17	PCR	Good/fair	Low
Aslani MM,2003 (35)	CC	Adult Children 1-79 yr	population based	F:1712, M: 1556	1998	3268	fecal	22	Serology	Good/fair	Low
Kargar M,2009 (36)	CS	Children < 5yr	diarrhea	F:278, M: 337	2006-2007	615	fecal	7	PCR	Good/fair	Low
Aslani MM,1998 (37)	CC	Adult Children 1-85 yr	Population based	F:1008, M:1000	1997	2008	fecal	98 VT	NSF LAT	Good/fair	Low
Zarringhalam M,2016 (16)	CS	UA	Diarrhea- E.coli Positive	UA	2013-2014	147	fecal	11	M-PCR	Poor	Moderate
Sadeghifard N,2002 (38)	CC	Adult children	Healthy diarrhea	UA	1999	1557	fecal	26	LAT	Poor	Moderate
Alikhani MY, 2013 (39)	CS	adolescent	diarrhea	F:75, M:112	2008-2009	187	fecal	6	PCR	Poor	Moderate
Abbasi P,2014 (40)	CS	Children < 2 yrs	diarrhea	F:9, M:19	2012	285	fecal	15	PCR	Poor	Moderate
Shams S,2013 (41)	CS	children	diarrhea	F:443, M:524	2008-2009	6500	fecal	27	PCR	Good/fair	Low
Dormanesh B,2015 (42)	CC	children	Diarrhea healthy	UA	2014-2015	480	fecal	54	PCR	Good/fair	Low
Zeighami H, 2015 (43)	CS	children	diarrhea	F:55, M:85	2011-2012	450	fecal	17	PCR	Good/fair	Low
Jomezadeh N,2009 (44)	CS	adult	diarrhea	F:23, M:77	2008	386	fecal	57	PCR	Good/fair	Low
Alizadeh AHM,2007 (45)	CS	adult	diarrhea	UA	2003	144	fecal	15	PCR	Good/fair	Low
Salmanzadeh-Ahrabi S,2013 (46)	CC	children	diarrhea	UA	2003	400	fecal	34	PCR	Good/fair	Low
Mohammadi-Sardo MR, 2017 (47)	CC	children	diarrhea	F:333, M:355	2014-2015	685	fecal	34	LAT	Good/fair	Low
Taghadosi R,2018 (48)	CS	Children, adult	diarrhea	F:180, M:215	2014-2015	395	fecal	5	PCR	Good/fair	Low
Alizade H, 2017 (49)	CS	UA	HIV Thalassemia	F:32, M:85	2014	117	fecal	36	PCR	Good/fair	Low
Alikhani MY, 2011 (50)	CC	children	Diarrhea healthy	UA	2003-2004	54 53	fecal	2	PCR	Good/fair	Low

CS = Cross Sectional, CC = Case Control, C = Cohort, SAT = Slide Agglutination Test, LAT = Latex Agglutination Test, TAT = Tube Agglutination Test

Statistical Analysis

The prevalence was calculated from the number of samples confirmed for STEC and total population in each study. We used the Cochran's Q test at the 5% significant level ($P < .05$) and the I^2 index to assess heterogeneity between the studies. According to the significant between-studies heterogeneity ($P < .05$), random effect model was used. In case that some studies didn't report their standard error and 95% confidence interval of prevalence rate, the binomial distribution was used to estimate the variance and 95% confidence interval for all included studies.

To estimate the pooled prevalence rate we used metaprop command in stata software (StataCorp, College Station, TX, USA). The metaprop commands was specific to binomial data and for proportions near boundaries (i.e., in this instance prevalence near to 100% or zero) which allows computation of exact binomial and score test-based confidence intervals by allowing Freeman-Tukey double arcsine transformation to stabilize the variances.[10] We used a random-effect model with invers variance weighing method to compute the odds ratio and 95% CI for comparing odds of developing diarrhea in patients with STEC compared to carriers. Subgroup analysis was done for different ages (children- adults), different periods of study, and the disease states. The possibility of publication bias was evaluated using Begg's test and Egger's test[11] and visually checked the funnel plot.[12] We used EndNote X7 to manage the records and reviewing the result

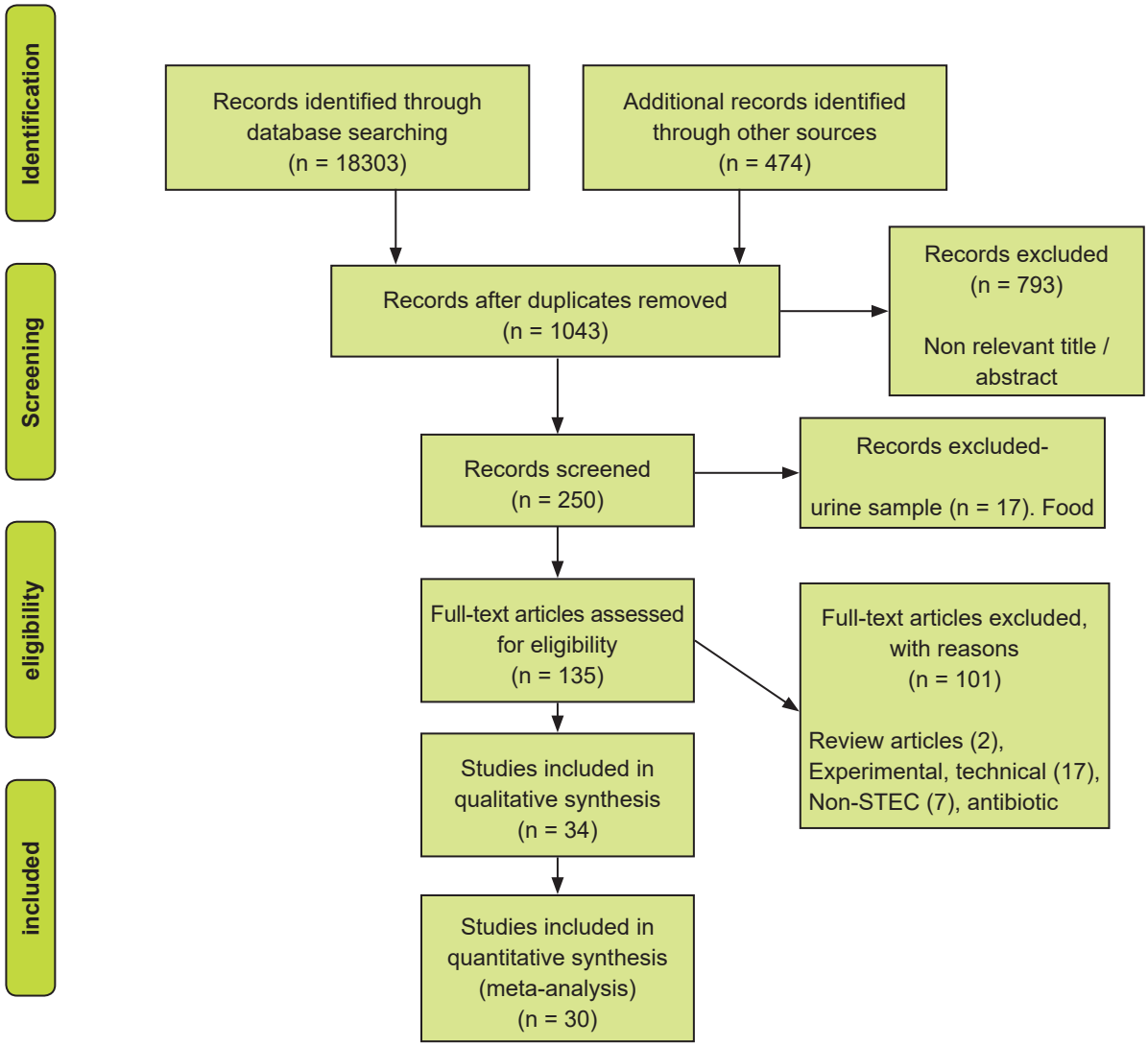

Figure 1. Flowchart for Selection of Manuscript STEC in Human with Gastroenteritis in Iran

of systematic search and Microsoft Excel 2010 to preparing data extraction sheet. We also used Stata11 (StataCorp, College Station, TX, USA) to perform statistical analysis.

RESULTS

Study Characteristics

A total of 30 potentially relevant articles containing 23379 samples were eligible for the final analysis. Of them 922 (3.17%) was positive for STEC. The design was cross sectional in 16(53%), case control in 13(43%), and cohort in one (4%). The specimen was feces in 27, and both feces and urine in one study.[13] One study just reported serotype of enterohemorrhagic E.coli O157, O26, O111.[14] Two studies did not confirmed serological detected STEC cases by PCR.[15,16] Median duration of 27 studies was 12 months (range 3 - 120 m). Gender was determined in 17 studies, with 4985 female and 5174 male (Table 1). A flow diagram of selection process according to the PRISMA flowchart is shown in Figure 1. The most common serotypes were O157:H7 (8.9%), O26 (16.26%) and O111 (18.43%). Shigatoxin (Table 2).

Publication Bias, Pooled Prevalence / Odds Ratio and Subgroup Analysis

There was no evidence of publication bias based on the results of Begg's test ($P > .05$) and Egger's test ($P > .05$) (Figure 2). The results of Chi-square test and I^2 statistics showed substantial heterogeneity among the studies that reported the STEC and risk of diarrhea in patients ($Q = 17.26$, $P < .001$ and $I^2 = 64.7\%$) and studies reported prevalence of STEC in Human Studies ($Q = 1647$, $P < .001$ and $I^2 = 98\%$). Consequently, the random effect model was used for analysis in this study.

Based on the random effect model, the pooled

Table 2. Shiga Toxin Genes Detected in Studies Between 1985 and 2017

Study ID	STEC (n)	STEC Gene (n)
Abbasi P, 2014 (40)	15	stx1 (2); stx2 (8); stx1, 2 (3); stx2, eaeA (2)
Akbari A, 2009 (28)	9	Stx1, stx2
Alborzi A, 2008 (32)	0	Not detected
Alikhani MY, 2011 (50)	2	Stx1, 2 (2)
Alikhani MY, 2013 (39)	6	STX+, eaeA-
Alikhani MY, 2007 (31)	39	Stx , Non-O157; H7
Alizade H, 2017 (49)	36	Stx1 (34), stx2 (1), stx1.eaeA (1)
Alizadeh AHM, 2007 (45)	15	Stx1, 2
Aslani MM, 1998 (37)	98	Stx1 (67); stx2 (24); stx1.2 (5)
Aslani MM, 2003 (35)	22	Stx1 (17); stx2 (4), stx1, 2 (1)
Aslani MM, 2007 (30)	14	Stx (12); non-O157 (2)
Aslani MM, 2008 (27)	86	stx
Aslani MM, 2009 (24)	29	Stx1 (28); stx2 (1); ehlyA (13); ast1 (7)
Bonyadian M, 2010 (25)	28	Stx1 (16); stx2 (4); stx1.2 (8); ehlyA (12)
Dormanesh B, 2015 (42)	54	Stx1 (54); stx2 (27); stx1.eaeA (35); stx2.eaeA (14), stx1, 2eaeA (11); stx1.eaeA. ehly (4)
Haghi F, 2014 (34)	17	Stx1 (7); stx2 (6); stx1.eaeA (1), stx2.eaeA (3)
Jomezadeh N, 2009 (44)	57	Stx1 (20); stx2 (28); stx1.2 (9)
Kargar M, 2009 (36)	O157:H7 (7)	stx1.eaeA (1)
Kargar M, 2014 (26)	104	STX1 (14); STX2 (31); stx1.2 (9); stx1.eaeA (12); stx2.eaeA (25); stx1.2.eaeA (13)
Mehrabiyan S, 2013 (23)	5	stx1 (3); eaeA (2)
Mohammadi-Sardo MR, 2017 (15)	34 (LA)	Not studied
Momtaz H, 2013 (33)	122	Stx1 (87); stx2 (12); stx1.eaeA (66); stx2.eaeA (38); stx1.2.eaeA (12); eaeA (75); stx1.eaeA.ehly (6)
Naeb-Agaie SM, 2006 (13)	3	stx2 (3)
Nahaie MR, 2007 (14)	0	None
Sadeghifard N, 2002 (38)	26	vt1 (18); vt2 (7); Vt1.2 (1)
Salmanzadeh-Ahrabi S, 2013 (46)	34	Stx1 (4); stx2 (19); stx2.eaeA (6); stx1.2.eaeA (1)
Shams S, 2013 (41)	27	Stx1, stx2
Taghadosi R, 2018 (48)	5	Stx1, stx2
Zarringhalam M, 2016 (16)	11	No VFG detected
Zeighami H, 2015 (43)	17	Stx1 (8); stx2 (9)

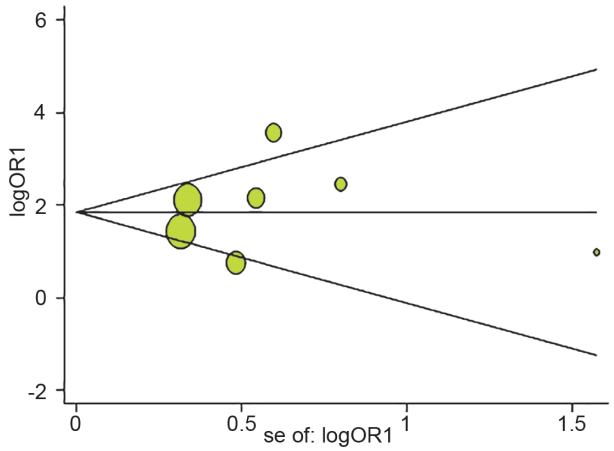

Figure 2. Begg's Funnel Plot for Assessing the Publication Bias

prevalence of STEC in human studies was 7% (95% CI, 5 – 11; I^2 = 98.3%) (Figure 3). In subgroup analysis, the pooled prevalence of STEC was 8% (95% CI, 4 – 13; I^2 = 97.6%) in children but 4% (95% CI, 2 – 7; I^2 = 97.7%) in adults (Figure 4).

The odds ratio of patients with diarrhea having had STEC was 7.1 times the odds of its having in healthy subjects (pooled OR = 7.06, 95% CI: 3.66 - 13.61; I^2 = 64.7) (Figure 5). Patients with bloody diarrhea were less likely to have positive STEC than patients with non-bloody diarrhea (pooled OR = 0.33, 95% CI: 0.10 - 1.02; I^2 = 73.8) (Figure 6). The odds ratio of males having had STEC was 0.9 (95% CI, 0.56 - 1.4; I^2 = 47%). Table 2 showed the stx genes detected by PCR or latex agglutination.

Sensitivity Analysis

In sensitivity analysis, to assess the effect of every study on the strength of association, the pooled odds ratio was calculated after excluded every study from meta-analysis. We found no significant difference between the pre-sensitivity pooled odds ratio for developing diarrhea (OR = 7.06, 95% CI: 3.66 - 13.61) and post-sensitivity pooled odds ratio after excluded each study from analysis. The lower and higher pooled odds ratio in sensitivity analysis was 5.45 (95% CI: 3.29 - 9.03) after exclude the Aslani et.al study and 9.07 (95% CI: 4.78 - 17.23) after exclude the Aslani et.al study, respectively (Table 3). We also repeat the sensitivity analysis

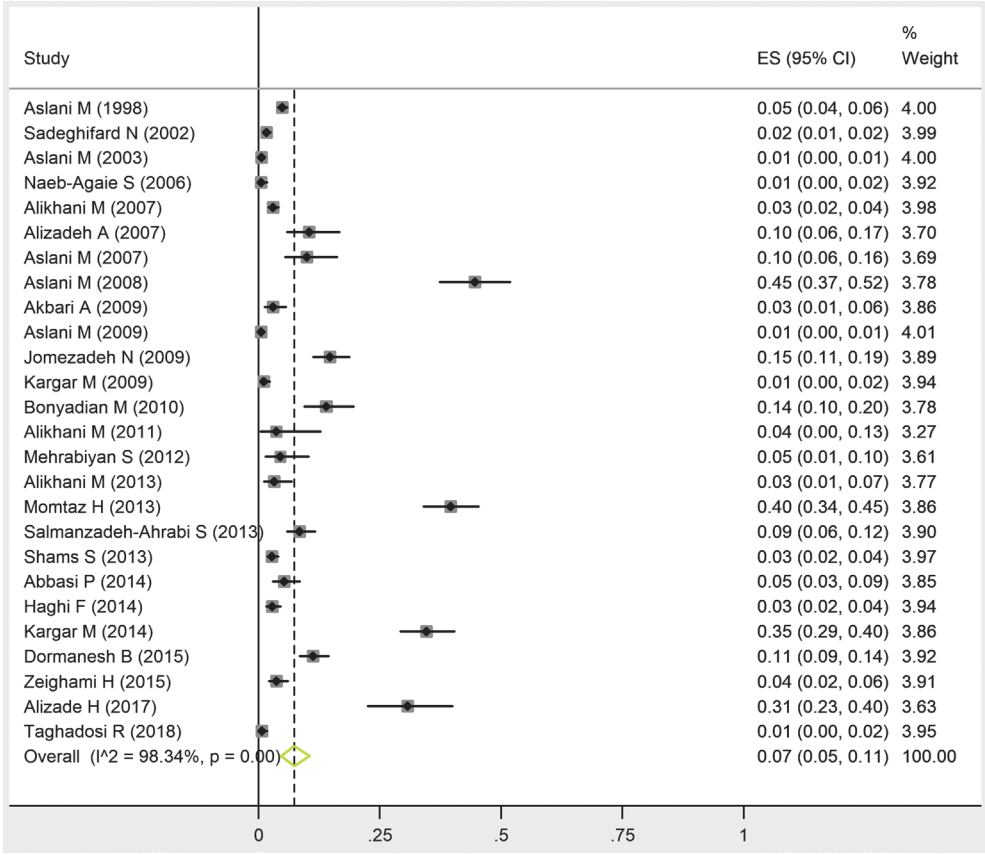

Figure 3. Pooled Prevalence of STEC in Human Studies between 1985 and 2016 in Iran

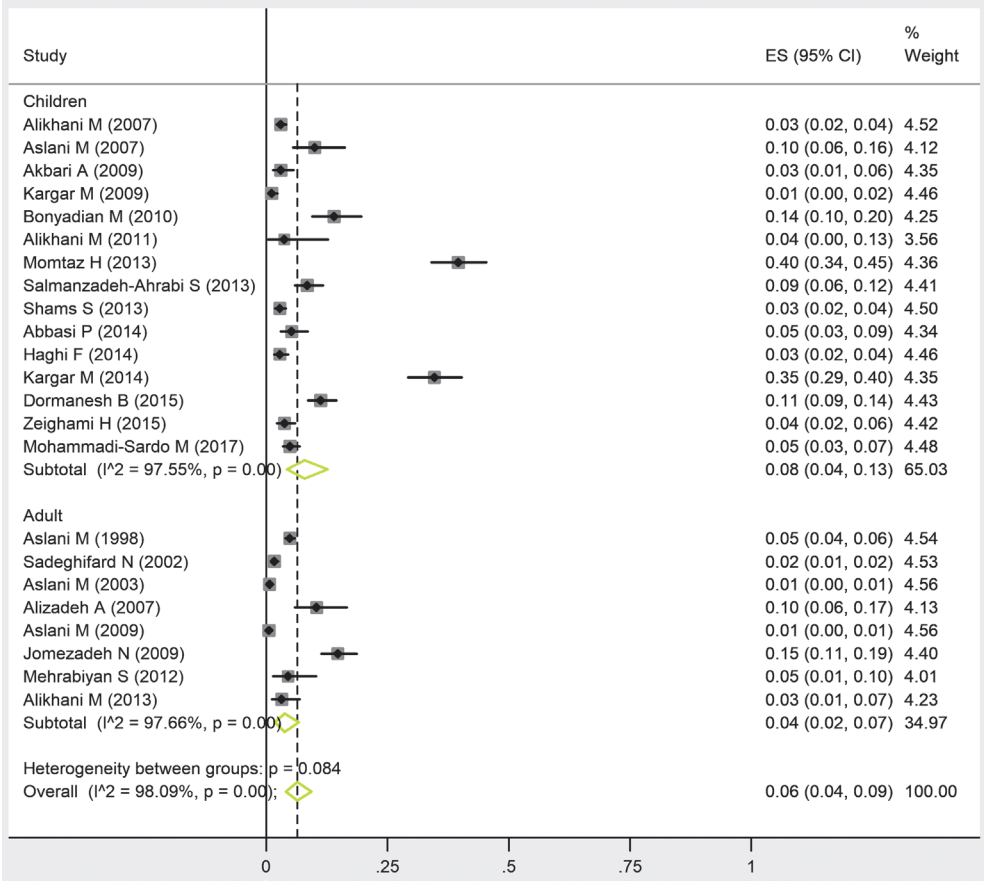

Figure 4. Prevalence of STEC in Children and Adults between 1985 and 2016 in Iranian studies.

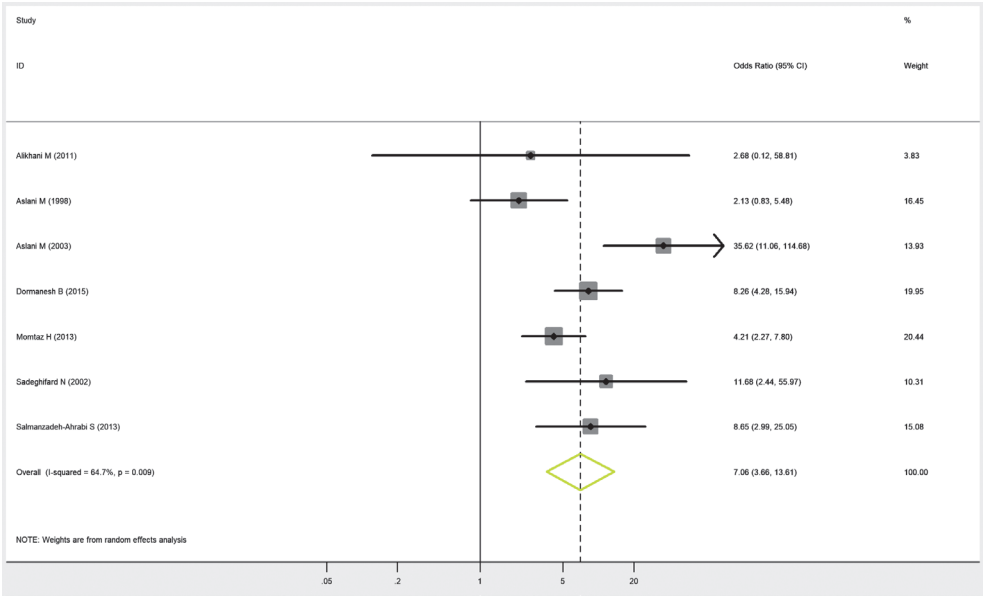

Figure 5. Forest plot of studies Comparing Odds of Developing Diarrhea in Patients with STEC Compared to Carriers.

in pooled prevalence estimations. We found no significant difference between the pre-sensitivity pooled prevalence in adult (P = 4%, 95% CI: 2 - 7) and children (P = 8%, 95% CI: 4 - 13) subgroups with post-sensitivity pooled prevalence after excluded each study from subgroup analysis (Table 3).

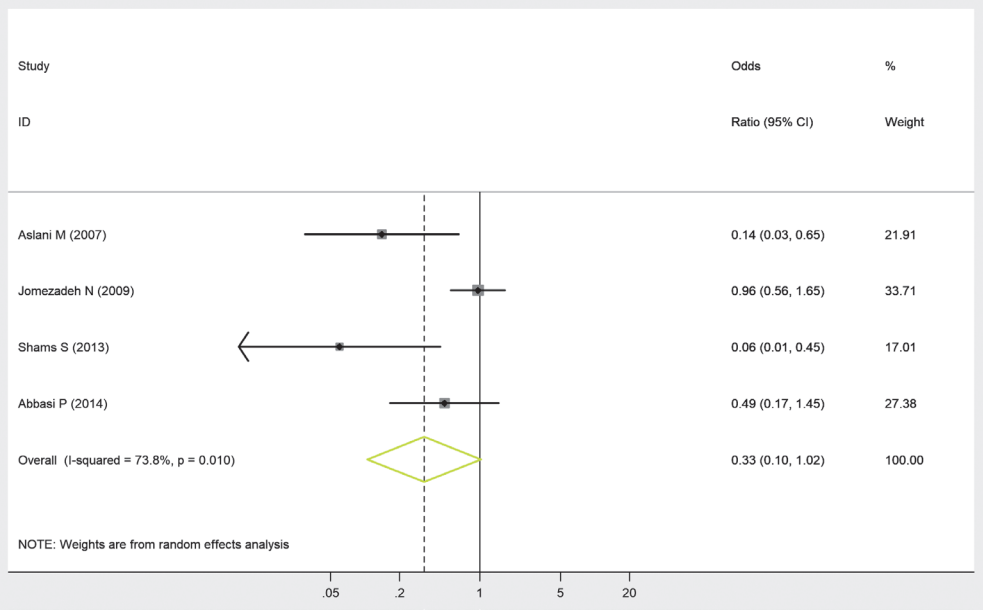

Figure 6. Forest plot of studies comparing odds of developing bloody diarrhea compared to non-bloody diarrhea in patients carrying STEC in Iran

Table 3. Result of Sensitivity Analysis for Assess the Effects of Every Study on Pooled Odds Ratio/Prevalence

Subgroup	Pre-sensitivity analysis			Post-sensitivity analysis			
	No.of studies included	Pooled OR/ prevalence (random effect)	95% CI	Upper & lower of EF*	Pooled OR/ prevalence (random effect)	95% CI	Excluded studies
Odds of Developing diarrhea	7	7.06	3.66-13.61	Upper	9.07	4.78-17.23	Aslani M (1998)
				Lower	5.45	3.29-9.03	Aslani M (2003)
Odds of Developing Bloody diarrhea	4	0.33	0.10-1.02	Upper	0.49	0.18-1.31	Abbasi P (2015)
				Lower	0.19	0.05-0.67	Shams S (2013)
Prevalence of STEC in Human Studies	26	7%	5-11	Upper	7.42	2.59-12.24	Aslani M (2009)
				Lower	5.89	1.14-10.64	Momtaz H (2013)
Prevalence in adult	8	4%	2-7	Upper	4.9%	2.80-6.90	Aslani M (2009)
				Lower	2.38%	1.38-3.37	Jomezadeh N (2009)
Prevalence in childeren	15	8%	4-13	Upper	9.62%	6.74-12.50	Alikhani M (2007)
				Lower	6.90%	4.89-8.86	Momtaz H (2013)

EF = Effect Size; the upper and lower limit of effect size (pooled odds ratio/prevalence) in post-sensitivity analysis after omitted every studies

DISCUSSION

This study showed the prevalence of STEC identified in human was 6.4% and it was higher in patients with gastroenteritis. Unfortunately only one study followed the infected patients for occurrence of HUS. In a case series of 78 STEC children in Canada, 13% developed HUS during seven days after initial presentation and half of them received antibiotics.[17] Another one-year study in France showed three percent of 658 stool samples of children with or without gastroenteritis were positive for STEC.[18] Similarly in Spain, 2.5 % of 5054 investigated cases were positive.[19] This review showed that the human contamination rate with STEC was higher in Iran than Europe, Canada, and America. Unfortunately, None of the studies had follow up to find the percentage of HUS development in Iranian subjects.

We found that the diarrheic patients had seven times more contamination with STEC than controls, In addition, the prevalence of STEC positive bloody diarrhea was fewer than non-bloody diarrhea. There were no gender differences in contamination rate but the prevalence was twice in children. A Peruvian cohort of 2212 subjects aged less than three years revealed the prevalence of 0.4% in diarrheic and 0.6% in control group.[20] This figure was 1.4% in diarrheic and 0.6% of healthy cases in

India.[21] The majority of studies were cross sectional; therefore, there was insufficient data for reporting the primary outcome of STEC- HUS because the most of them had no follow up or did not consider this outcome in the study design. Similarly there was no follow up for the rate of renal failure post STEC gastroenteritis. In addition, the heterogeneity of study groups (diarrheic, healthy, HIV, E.coli positive patients) made another limitation of this review. This review showed that the contamination rate in non-bloody diarrhea with STEC is high. Many laboratories consider E.coli as a normal flora without proceeding further molecular analysis. The Sorbitol- MacConkey agar (SMAC) was the main media for detecting E.coli. Recent study by Shinldet et al showed that a subset of E.coli O157:H7 might not be identified by SMAC agar culture, and concomitant use of SMAC agar and Enzyme immunoassay improves the rate of microorganism detection.[22]

CONCLUSION

The identification of STEC is high in patients with gastroenteritis. It should be considered in evaluation of those who presents with non-viral diarrhea. In the case of detection E.coli in the stool culture, further assessment in order to identify the shigatoxin is recommended.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

None

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