The Prevalence and Incidence of Hemolytic Uremic Syndrome in Iran, a Systematic Review and Meta-analysis

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HUS is a leading cause of AKI in infants. Though new classification of HUS is based on underlying disease, it traditionally defines as diarrhea positive (typical) and negative (atypical). We have no figure of the incidence and prevalence of HUS, the underlying disease and the outcome in Iranian patients. This meta-analysis of Iranian studies deals with this matter.

We used relevant medical search engines and national databases from 1985 to 2019. We searched manually to detect admissible cross references. All studies assessed for the aspects and the risk of distort by three appraisers. Metaprop package of STAT applied to calculate point prevalence, proportion, and incidence with 95% confidence intervals.

A total of 27 articles and one abstract of congress containing 7084 cases met all the inclusion criteria and qualified for the final analysis. Considering 1397 patients with HUS over 33 years of study, the pooled prevalence was 28% (95% CI: 15 to 44) and 18.38 pmp (0.55 pmp/y). In children less than 15 years, the prevalence was 79.82 pmp (2.41 pmp/y). Between 1985 and 2019, atypical HUS was identified in 488 patients with the prevalence of 27.88 pmp (annual prevalence of 0.84 pmp/y of children aged less than 15 years old). The incidence was 9.4 pmp (0.28 pmp/y), contributed to 9.9% (95% CI: 3 to 20) of AKI, and 5.48% (95% CI: 3.5 to 7.9) of CKD and ESRD. The rate of HUS diagnosis was increasing during the previous four decades. HUS consists of a significant number of AKI and ESRD. It needs further prospective longitudinal study.

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Review

INTRODUCTION

Hemolytic uremic syndrome diagnosed clinically by hemolytic anemia, the presence of schistocytes in peripheral blood smear, reduced platelet count, and acute kidney injury (AKI).[1] Atypical HUS (aHUS) is consistently used for describing diarrhea negative HUS in infants and children,[2] although one third of them have diarrhea as a provoking agent before presentation. Many countries have a strategy to confirm serologically or genetically the underlying disease. This policy helps to stratify the management accordingly. Early decorous management prevents the co morbidities involving kidney, heart, brain, and pancreas and reduces the

mortality.[3] The aim of this study was to find the incidence and prevalence of HUS, in addition to find the etiology, and the outcome of patients in Iran. Accordingly, we used the old terminology to compile evidence.

There are few registries for HUS in the world including global aHUS registry under a pharmacy license enrolled 516 cases from 16 countries and the five years outcome of the safety report of new anti-CH50 monoclonal antibody in ever treated vs. never treated among 1321, Turkish pediatric aHUS registry that reported the demographic and outcome and the underlying disease of 146 aHUS children.[4-6] Iranian registries for HUS are under construction (ID number: 98-1-37-14220) and a pilot genetic evaluation of aHUS is underway (ID number: 96/8/22-18). But this systematic review is a prerequisite for both ongoing projects. The aim of this study was to find the prevalence and incidence of HUS, the causative, and the outcome in Iran.

MATERIALS AND METHODS

Protocols and Registration

The planned systematic review is registered with the International Prospective Register of Systematic Reviews (PROSPERO), Review Registration number: PROSPERO 2017 CRD42017059086 is available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID = CRD42017059086. The Ethic code was IR.IUMS.REC 1396.31405. The full protocol had already been published in journal of Comprehensive Pediatrics.[7]

Study Selection

Criteria for Including Study. Systematic review or meta-analysis, longitudinal and cohort studies, cross-sectional, case-control, epidemiological studies, conference proceedings, thesis or unpublished data were considered for examination. Experimental studies, narrative reviews, and case reports, and thrombotic thrombocytopenic purpura cases were excluded.

Patients, Subjects, and Animals. All studies about HUS independently of renal biopsy.

Intervention / characteristic sought. The definition of HUS is microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. All cases with atypical or diarrhea negative and positive HUS or thrombotic microangiopathy included for assessment. Microangiopathic hemolytic anemia is identified by hemoglobin less than 5th percentile for age,[8] regardless of reticulocyte count, the presence of traumatized RBC (schistocyte, helmet, and burr cell (> 1%)),[9] LDH > 500 IU, so far as coombs tests were negative. Thrombocytopenia (platelet < 150000/ microL), and renal injury was delineated by serum creatinine more than 1.5 to 2 times baseline for age.[10]

Study Characteristic. The primary outcome was to identify the proportion of atypical HUS and the secondary outcome was the final outcome of aHUS including ESRD, Morbidity, death, or not otherwise specified. Studies issued between January 1985 and January 2019 took into account. The language was restricted to English and Persian. Merely published papers about Iran or Iranian population took into account. The report was accomplished according PRISMA guideline.[11]

Search Strategy

Literature Search. We categorized the browsers to following domains: 1) The trusted medical search engines (Web of Sciences, PubMed, Google, Google Scholar, OVID, EMBASE, and SCOPUS), 2) Iranian scientific search engines (health. barakatkns. com, MagIran, SID, IranMedex, and dociran), 3) Database of thesis, projects, congress processing in Iran (ganj.irandoc, PDFiran, database in each medical university). 4) We attempted to acquire the misfield features (by hand searching for cross-references, international, regional, or local websites of congress, make contact with the known Persian researchers adept in HUS). NH scanned for possibly eligible studies, FJ, MS, SH individually assessed whether the studies met the inclusion criteria. Before the final analyses we repeated the probe for the latest passable studies to be involved in the review. Table 1 shows the search strategy. Three reviewers assessed independently the quality (by STORBE) and the risk of bias (by Hoy *et al.*) of all papers.[12-13] Dispute between arbiters solved by agreement or by referee (NH).

Data Extraction. The ensuing items and data were collected from the articles:

bibliographic information of the paper, sample size, patient information (age, gender), etiology, the province of study, the duration of follow up, and upshot (healing, recurrence, demise, not mentioned). We corresponded with the authors in the case of missing data in the report.[14-16]

Table 1. Description of Search Strategy

Search Element	MEDLINE / EMBASE / PsycINFO	Other Databases
	Thesaurus Exploded	**Hemolityc Uremic Syndrome (kw, ti, ab) (AND)**
Hemolytic-Uremic Syndrome (AND)	Atypical Hemolytic Uremic Syndrome	Iran (kw, ti, ab)
	Thrombotic Microangiopathy	
	Glomerulonephritis	
	Acute Kidney Injury	
Morbidity (OR)	Morbidity	
	Dialysis	
	Chronic Renal Disease	
	Renal Dialysis	
	Renal Insufficiency Chronic	
	Mortality	
Iran (AND)	Iran	

Data Analysis. If the studies could not be congregated: We utilized both the Chi-squared test and the I-squared statistic to gauge diverseness between the researches in effect measures (I-squared value > 50% indicate substantial heterogeneity). We did subgroup analysis for different ages (children - adults), designated as AKI, glomerulonephritis, or CKD and dialysis. Because of extreme proportions

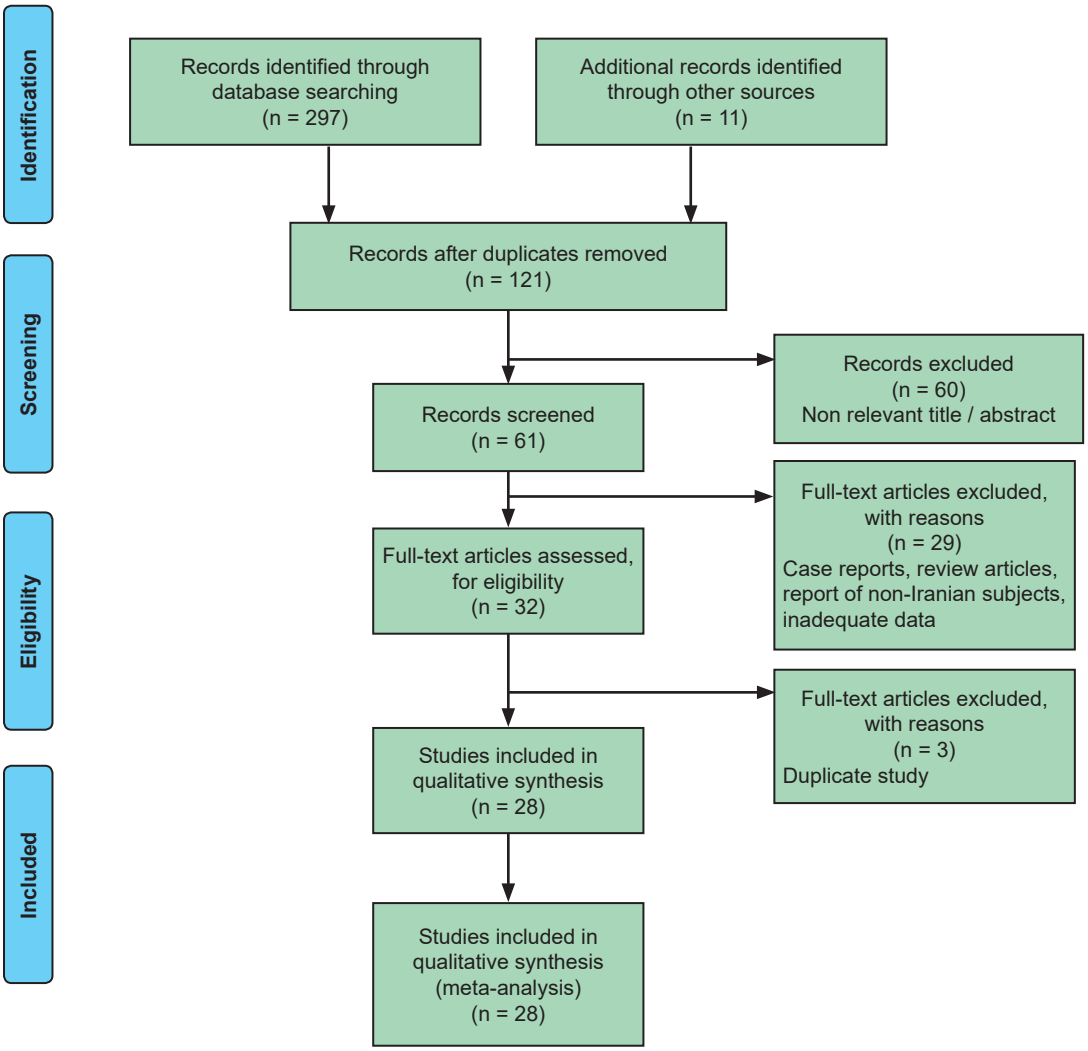

Figure 1. It shows flowchart of selection of relevant studies about HUS in Iran.

(0% to 100%), we utilized to estimate the pooled prevalence rate. We used metaprop command in stata software (StataCorp, College Station, TX, USA). The pooled prevalence was calculated by the number of cases (death or alive) per the total number of population study. The incidence was new cases (alive) per the total number of population study.

RESULTS

Study Characteristics

Study Screening and Selection. The primary literature survey provided 40908 references, which were cut down to 308 after abolishing non-relevant articles. Subsequently initial abstract audit, 61 articles were left. Additional 29 articles were excluded after assessing full-texts. After removing duplicate publications, a total of 27 articles and one abstract of congress containing 7084 patients met all the inclusion criteria and were eligible for the final meta-analysis (Figure 1). Table 2 represents the summary of the included studies. About 39.5% of articles had high risk of bias and 46.3% had good quality. We included all poor and good quality articles in this study.

Pooled Prevalence / Odds Ratio

Proportion of HUS. To 7084 populations of studies, 1397 had HUS. Considering Iran population of 76 million that 23% (17.5 millions) were less than

Table 2. Summary of Studies in Iran About HUS

Study ID	Design Period	Sample	Population	Age (SD), y	Gender (M / F)	Outcome	STORBE / BIAS
Mehrazma M, 2011[17]	Cohort (1995-2005)	THUS (102) aHUS (29)	HUS	6 (4.68)	21 / 8	HTN (3) Death (7) CKD-D (7)	15 / 7
Mehrazma M, 2007[18]	Cross-sectional (1995-2005)	THUS (102) aHUS (28)	HUS	6 (4.68)	20 / 8	Death (7)	14 / 7
Mehrazama M, 2007[19]	Case-control (1995-2005)	THUS (102) aHUS (28)	HUS, Kidney Biopsy	6 (4.68)	20 / 8	Short Outcome	15 / 7
Karimi M, 2006[20]	Observational (1991-2003)	THUS (136)	HUS	3.5 (3)	52 / 49		12 / 8
Sabzi A, 2007[21]	Observational (1991-2003)	THUS (136) D + ve (84)	HUS, TTP	3.5 (3 mo - 35 y)	52 / 49	HD (12) HTN (10) Seizure, Neurology (7) Death (20) CKD-D (12)	14 / 7
Hosseini S, 2014[22]	Cross-sectional (2010-2013)	THUS (273) aHUS (273)	HUS	27.3 (1 y - 87 y)	150 / 123		16 / 8
Ataie N, 2004[23]	Case Series (1982-2002)	THUS (80) aHUS (19) D + ve (61) (bloody (51))	HUS	3.21	41 / 39	Death (28) CKD (76)	12 / 6
Hashemi GH, 1994[24]	Cohort (1986-1991)	THUS (70) aHUS (5) D + ve (35)	HUS	< 1 y to > 5 y		PD (40) Death (15) CKD-D (6) HTN (6)	12 / 6
Derakhshan A, 2002[25]	Observational (1988-1998)	THUS (99) aHUS (6) Bloody D (74)	HUS	2.29 (2.87)	45 / 35	HD (1) PD (54) Death (12) CKD-D (10)	10 / 6
Hooman N, 2007[26]	Cross-sectional (1999-2004)	THUS (104) aHUS (23) D + ve (81)	HUS	4 (3.62)	70 / 34	HTN (36) Death (18)	14 / 7
Otukesh H, 2008[27]	Cohort (1999-2004)	THUS (92) aHUS (23) D + ve (69)	HUS	4.09 (0.39) (Birth to 16 y)	63 / 29	HTN (18) CRF (6) Death (3)	17 / 7
Bodaghi E, 1989[28]	Cross-sectional (1976-1985)	TBiopsy (411) HUS (6)	GN	7.4 y (1.5 - 18)	3 / 3		14 / 6
Antonovych T, 1999[29]	Cross-sectional (1981-1994)	TBiopsy (713) HUS (3)	GN	1 y to 10 y	UA	UA	11 / 6

Table 2. Continued

Study ID	Design Period	Sample	Population	Age (SD), y	Gender (M / F)	Outcome	STORBE / BIAS
Madani A, 2003[30]	Cross-sectional (1986-1995)	TBiopsy (408) HUS (19)	GN, Kidney Biopsy	3.66	13 / 6	HTN (17)	16 / 7
Hooman N, 2009[31]	Cohort (1993-2006)	TCKD (120) aHUS (13)	CKD	< 14 y	62 / 58	PD (13)	17 / 8
Derakhshan A, 2004[32]	Cohort (1993-2000)	TCKD (1358) aHUS (10) D + ve (49)	CKD	6.5 (4.7) 1 mo to 16 y	709 / 649		11 / 5
Hooman N, 2014[33]	SR (2000-2004)	TAKI (562) HUS (102)	AKI	Child Neonate	UA	UA	15 / 7
Madani K, 2001[34]	Cross-sectional (1991-1999)	TCKD (166) HUS (13)	CKD	Child		CKD-D (13)	
Ataie N, 2016[35]	Cross-sectional (1991-2014)	TCKD (372) HUS (17)	CKD	7.71 (3.94)	186 / 186	HD (48%) PD (6.6%) Death (13.5%)	15 / 5
Otukesh H, 2006[36]	Cross-sectional	TAKI (267) HUS (72)	AKI	1 mo to 16 y		Death (18) HTN (1)	14 / 6
Gheissari A, 2012[14]	Observational	TAKI (180) aHUS (4) D + ve (20)	AKI	5.28 (6.3) y	14 / 8	HD (2) PD (18) Death (2) CKD-D (3)	9 / 4
Derakhshan A, 2002[37]	Cross-sectional (1999-2000)	TAKI (50) aHUS (1) D + ve (3)	AKI	6.38 (1.92) 3 mo to 15 y	37 / 13	Death (.00) CKD-D (1)	8 / 5
Ahmadzadeh A, 2010[38]	Observational (2003-2006)	TAKI (113) HUS (3)	AKI	< 2 mo to 15 y	77 / 36	UA	7 / 5
Tavasoli A, 2019[39]	Observational (2001-2015)	THUS (125) aHUS (32) D + ve (32)	HUS	43 (5 - 14)	33 / 25	Death (16)	15 / 5
Saddadi F, 2010[40]	Observational (2000-2002)	TBMT (378) aHUS (7)	BMT	18 (13), 3 y to 59 y	224 / 154	HD (.00) Death (00) CKD-D (.00)	16 / 7
Akhavan Sepahi M, 2011[15]	Observational (2000-2006)	TGN (94) HUS (2)	GN	8.7 (2.7) (1 to 15 y)		HD (1) Death (1)	11 / 6
Mortazavi F, 2010[41]	Observational (1999-2009)	TCKD (115) HUS (2)	CKD	8.1 (3.5) y (4 mo to 14 y)	61 / 42	CKD (2)	11 / 6
Fallahzadeh MA, 2015[42]	Cross-sectional (2011-2013)	TAKI (256) HUS (2)	AKI, Death in PICU	4.3 (5) y		Death (2)	14 / 7
Naghavi MA, 1998[16]	Observational (1992-1995)	TGN (100) HUS (1)	Hematuria	UA			14 / 7
Afshin A, 2018[43]	Cross-sectional (2005-2017)	HUS (76) aHUS (37) D + ve (6)	HUS	<18 y	40 / 36	Death (4) Dialysis (53)	7 / 5

15 years old, we estimated the incidence of HUS. *Primary Outcome.* The pooled prevalence was 28% (18.38 pmp and annual prevalence of 0.55 pmp, Figure 2). The incidence was 9.4 pmp (annual incidence 0.28 pmp/y). In children less than 15 years, the prevalence was 79.82 pmp (prevalence of 2.41 pmp/y). Atypical HUS was identified in 488 patients (pooled prevalence 16% (95% CI: 4.5 to 31, I^2 = 99%) between 1985 and 2019. Adjusting to total population of children, the estimated prevalence was 27.88 pmp and the annual prevalence was 0.84 pmp of children aged less than 15 years old (Figure 3). For diarrhea positive HUS, none of them studied for Shiga-toxin E.coli. The estimated pooled prevalence was 37.9% (95% CI: 15.5 to 63.4, I^2 = 99%). A pooled prevalence of HUS death rate was 7.8% (95% CI: 3.7 to 13, I^2 = 94%).

Subgroup Analysis. The pooled prevalence of dialysis dependent HUS was 24% (95% CI: 7.8 to 45.8, I^2 = 98%; Figure 4).

HUS contributed to 9.9% (95% CI: 3 to 20, I^2 = 96.5%) of 1428 cases presented with AKI, and

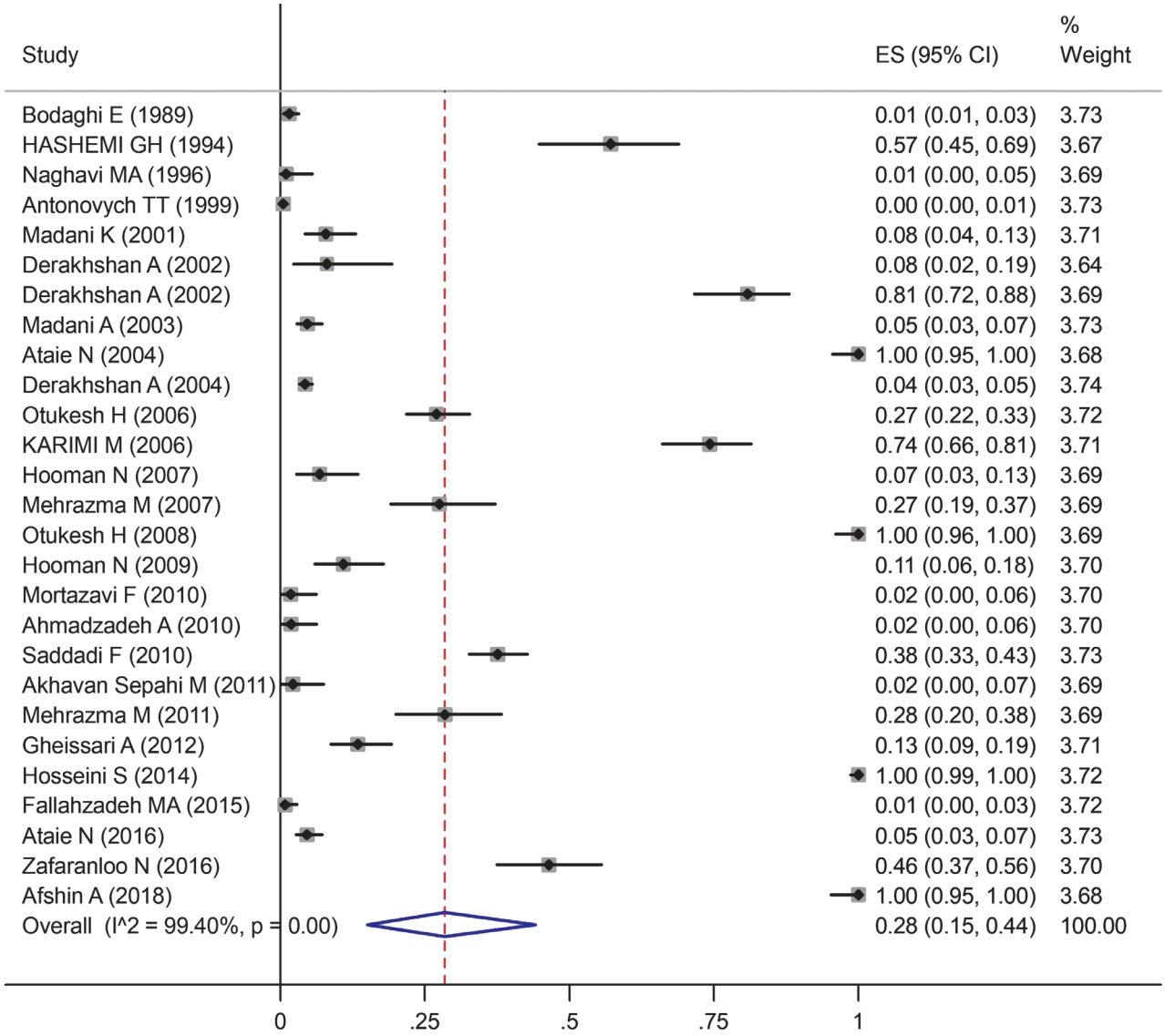

Figure 2. It mentions forest plot and meta-analysis of HUS.

5.48% (95% CI: 3.5 to 7.9) of 2131 cases of ESRD in any event. The pooled prevalence of death rate was 7.8% (95% CI: 3.7 to 13, $I^2 = 93\%$). The odds ratio of death in aHUS was 1.2 (95% CI = 0.34 to 4.2, z = 0.9; $I^2 = 38\%$) times the odds of its having diarrhea associated HUS.

The proportion of HUS was 7.9% (95% CI: 0.36 to 24, $I^2 = 98\%$) before 2000, increased to 33% (95% CI: 15.3 to 53.8, $I^2 = 98.6\%$) till 2010 and then slightly reduced to 24.1% (95% CI: 3.4 to 55.7, $I^2 = 99.5\%$) after year 2010.

Bias. Of 30 articles, 13 studies were about HUS presentation and outcome, and the rest of studies were about glomerulonephritis (n = 5), AKI (n = 6), CKD (n = 5), and bone marrow transplantation (n = 1). Figure 5 showed Funnel Plot of standard error by proportion of HUS.

Sensitivity Analysis. We assessed the sensitivity analysis in pooled prevalence estimations. We found no significant difference between the pre-sensitivity pooled prevalence with post-sensitivity pooled prevalence after excluded every study from analysis

DISCUSSION

This meta-analysis displayed that HUS had a pooled prevalence of 28% (95% CI: 15 to 44) over three decades (0.55 pmp/y). Nevertheless, not all cases with HUS reported this figure presumably underrated. Regrettably, the diagnosis of underlying

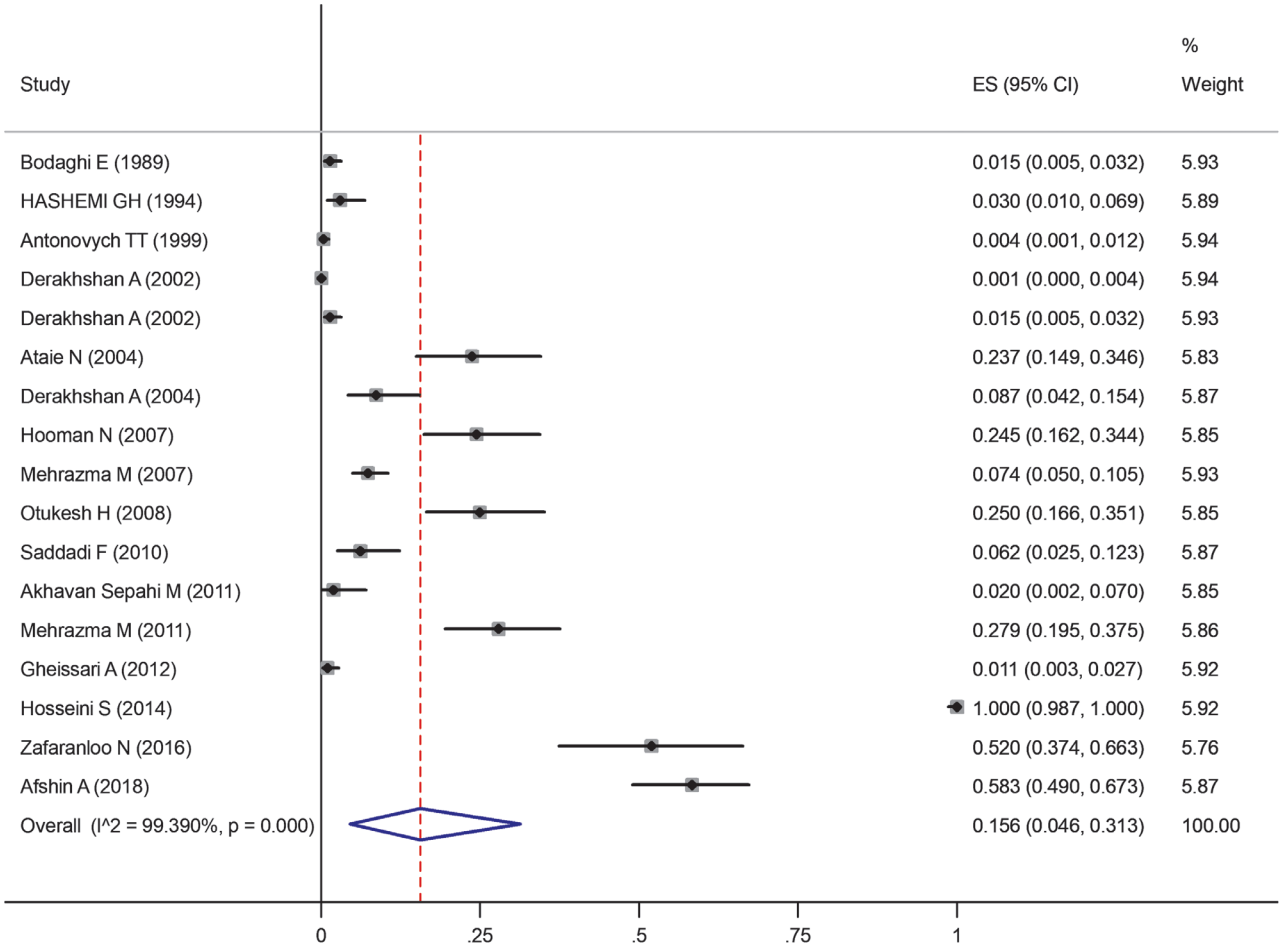

Figure 3. It shows forest plot and meta-analysis of diarrhea negative HUS.

disease was mainly based on complement level, the age of presentation, family history, and the recurrence of disease in index. Hence, the study was incompetent to distinguish between the ultra-rare complement dysregulation and common post-infectious HUS. We used traditional terminology of atypical (diarrhea negative) vs. typical (diarrhea positive). Thus, we demonstrated a pooled prevalence of 16% for atypical HUS (diarrhea negative) and 38% for diarrhea positive HUS.

In this study we gathered 1397 cases with HUS. Mentioning to the report of other registries we emphasize that this belittled figure did not constitute the true affected population in Iran. According to an Indian nationwide registry, 781 patients with aHUS aged less than 18 years announced an annual incidence of 0.13 pmp.[44] Furthermore, Turkish registry piled up retrospectively and prospectively the input of 146 aHUS during three years.[45] Data from North part of Italy reported 101 cases of HUS over 10 years including both STEC and aHUS. The average incidence was 6.3 cases pmp/y in children less than 18 years old.[46]

Despite none of these 1397 patients with HUS had been confirmed or investigated for Shiga-toxin associated E.coli, 38% had a prodromal diarrhea. This review was inconclusive for underlying disease of HUS. In another meta-analysis the pooled prevalence of STEC in Iran was 7%. Surprisingly, the odds of having STEC in diarrheic patients was 7.06 times and the bloody diarrhea was less likely to have positive STEC (OR = 0.33).[47] The pooled prevalence of STEC associated UTI was 3.46% .[48] None of them had follow up for reporting HUS. Early consideration for STEC (stool culture and serology test) before resorting to any antibiotic might assist to heighten the responsiveness of screening for this bacterium.

HUS is a leading cause of AKI in children and atypical form is associated with morbidity such

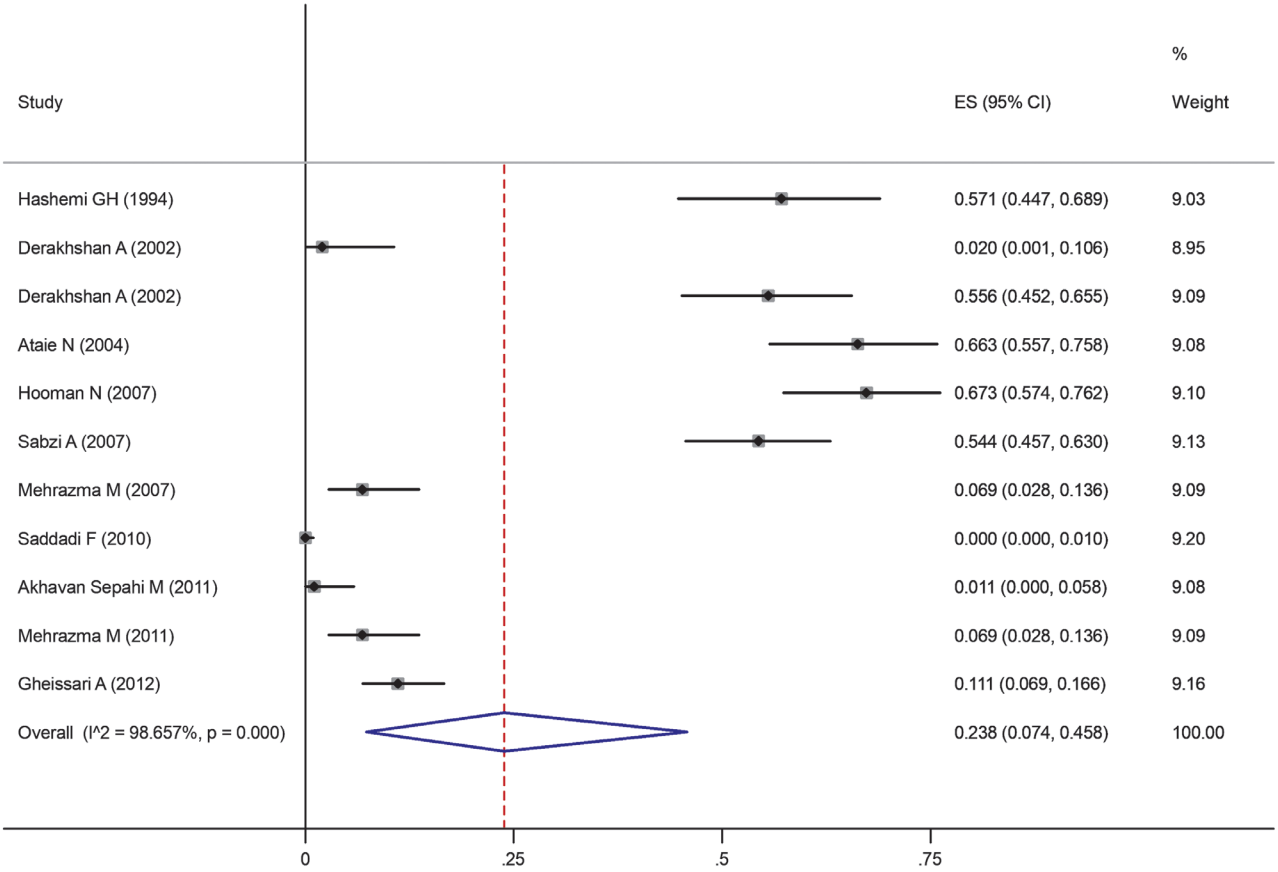

Figure 4. It mentions forest plot and meta-analysis of HUS required dialysis.

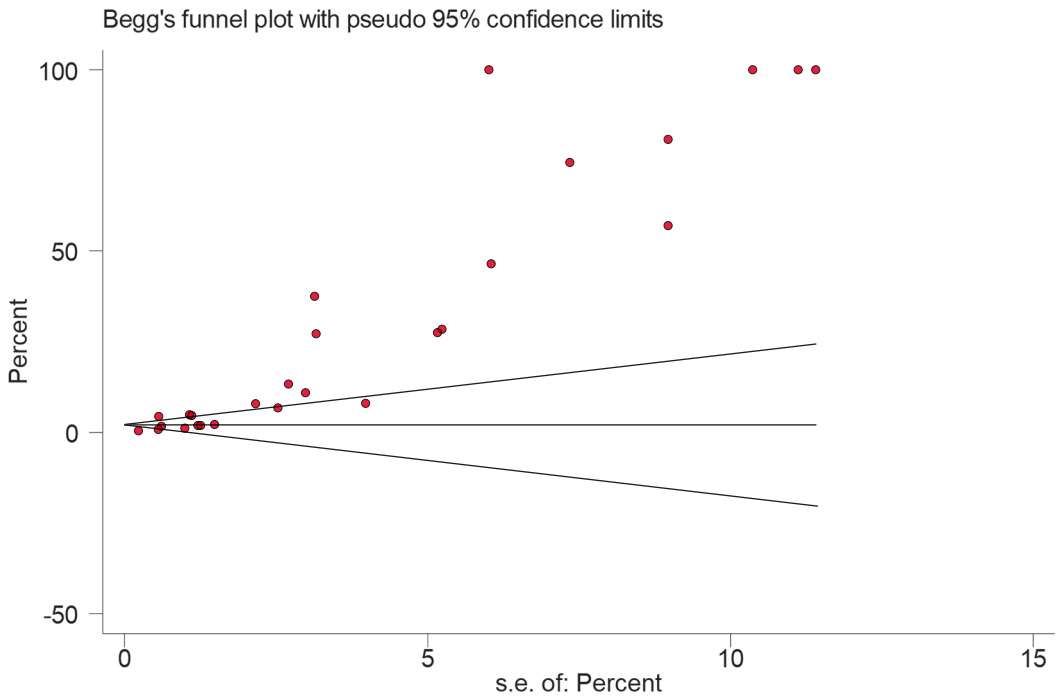

Figure 5. It shows funnel plot of standard error by proportion of HUS.

as ESRD or neurological abnormalities. Taking into consideration that renal transplantation in HUS patients has a high risk of recurrence without appropriate medication.[49] According to the present systematic review 24% of HUS cases are on dialysis. HUS promoted to 10% of AKI and 5.5% of CKD and ESRD in Iran. In a cohort of 118 cases of aHUS in Japan, ESRD occurred in 12%.[50] The recurrence of disease and handling of aHUS complications have a huge impact on the quality of life of the child, family, and on economy.

HUS has renal and extra renal involvement. The early diagnosis of underlying disease and appropriate treatments improve the outcome and renal function and lessen non-essential expenses. Atypical HUS is an orphan life threatening genetic illness.[51] In addition to clinical and laboratory assessment, genetic study is mandatory to amid correct diagnosis. This review disclosed that none of the preceding studies was lucky enough in perceiving STEC. We suggest to pay attention to diagnostic approach of HUS.[52,53]

The limitation of this study was the poor strength of enrolled articles, lack of genetic confirmation of the type of HUS, no standard evaluation of diarrhea induced HUS for microorganism, and short follow ups. Moreover, the incidence and prevalence of HUS (aHUS, D + HUS) were underestimated, as long as all patients with HUS have not been reported. Hence the true incidence and prevalence might be higher than the figure presented in this systematic review. In order to find how many patients truly profit from diagnostic tests and new treatment of HUS an ongoing cohort study and designing a national registry is required.

CONCLUSION

The rate of recognition of HUS was expanding during the antecedent four decennium HUS embraces noteworthy numeral of AKI and ESRD. For more conclusive results, imminent investigation is mandatory.

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CONFLICT OF INTEREST

None.

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