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Hepatitis C Virus Prevalence among Patients with Beta Thalassemia Major in Iraq: A Systematic Review.

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Abstract
Background: Hepatitis C virus (HCV) infection was characterised by its pandemicity. The disease was the most common post-transfusion infection. Global HCV prevalence varies regionally, and within countries. HCV infection was common in certain community settings including thalassemia.
Objective: to determine HCV infection in subjects with beta thalassemia major in Iraq.
Methods: The search includes Pubmed and Google Scholar data. The key words used for search are Hepatitis C, HCV, Hereditary blood diseases, Thalassemia, and Iraq.
Results: The search retrieved 23 studies, however, 5 studies were excluded because not fulfil the inclusion criteria. Fig.1 shows the flow diagram. Eighteen studies fulfilled the inclusion criteria which composed of 5451 patients with thalassemia were included in the systematic review. The year of data collection in the studies was between 2000 to 2020. The pooled HCV prevalence in beta thalassemia major was 20.49%.
Conclusion: The study indicated high HCV prevalence in beta thalassemia major in Iraqi community. Third generation ELISA test as screening test must be replaced by PCR and not restricted for positive ELISA as a confirmatory test. Relay on ELISA may not detect cases which was not seroconverted. National large-scale, well designed program that cover national and all governorates is warranted. Collaboration between medical colleges and regional health authorities is required and it was essential for national program success.
Keywords: Hepatitis C, HCV, Beta thalassemia, Iraq, Systematic review, Blood transfusion.

Introduction

Hepatitis C virus (HCV) infection was characterised by its pandemicity [1], with a chronic natural course in 3% of the global population [2]. Untreated cases of HCV infection will develop chronic liver diseases and cirrhosis in 14% to 45% during a period of 20 years later to infection acquisition [3]. The global prevalence of HCV was with a range of 0.4% in Germany to 22% in Egypt [4]. Additionally, the prevalence rate in the Eastern Mediterranean is with 1% to22% [4]. HCV was endemic in Arab countries and the prevalence is classified in

to 4 category, low (1-1.9%, Libya, Lebanon, Syria, Tunis, Bahrain, Oman, Kuwait and Saudi Arabia); Moderate (2.0-2.9%, Gaza Strip, Mauritania, Yemen, and Algeria); High (3-3.9%, Iraq, Sudan, UAE), and very high (>4%, Qatar, Jordan, Morocco, and Egypt) [5]. In Iraq, the prevalence rate was with range of 0.32% to 7.1% in general population [1,6,7]. However, general population are prone to HCV infections, certain medical or social groups are the target of HCV infection [8]. HCV was a blood born viral infection [9] and thus blood transfusion is the main route of HCV transmission in the community [10, 11].

Multiple (repeated) blood transfusion for a potential risk factor for acquisition of HCV infection especially in children as HCV prevalence was relatively low [12, 13]. Previous studies in Iraq reported HCV infection in children with inherited blood disorders who received repeated blood transfusion [12,14,15]. A child with Beta thalassemia major developed severe anaemia 6 months after birth and thus repeated blood transfusion is an important arm in their management protocol [16]. Global population carrier rate for thalassemia genetic mutation is about 1-5% [17]. Thalassemia highly prevalent in Middle East, Mediterranean, East and Southeast Asia and Indian subcontinent. However, now thalassemia is increased in North America and Europe as an outcome of migration and thus the disease at present from global health problem [18]. In Iraq, thalassemia prevalence was with a range of 3.7% to 6.5% [19-21]. Thus up to 6.5% of the Iraqi general population with thalassemia are at risk of getting HCV infection as an outcome of multi blood transfusion. To date no effective vaccine was developed to be used for HCV prevention and control and thus HCV infection remain a major health care problem in Iraqi individuals who receive multiple blood transfusion. This study performed aiming to determine HCV infection in subjects with beta thalassemia major in Iraq.

Materials and methods

Search strategy

This study conducted on the basis of " Preferred Reporting Items of Systematic Reviews and Meta-Analysis" PRISMA guidelines [22]. The search includes Pubmed and Google Scholar data. The key words used for search are Hepatitis C, HCV, Hereditary blood diseases, Thalassemia, and Iraq.

Inclusion and exclusion criteria

The inclusion criteria were:

1. HCV prevalence among Iraqi community.
2. Studies that deal with repeated blood transfusion.
3. Studies written in English.
4. Observation studies such as case-control, cross-sectional, retrospective and prospective.
5. Studies used Recombinant Immunoblot Assay (RIBA), Polymerase Chain Reaction (PCR) for viral particle detection and 3rd generation Enzyme Linked Immunosorbent Assay (ELISA) for HCV antibody detection.

The exclusion criteria were:

1. Studies in non-Iraqi population.
2. Studies that performed in blood disorders rather than thalassemia.
3. Studies performed in other risk groups.
4. Books, review, case reports, conferences abstracts, case-series, and editorial comment.

Then selected studies were reviewed. The search included studies up to December, 2020. Five studies excluded from analysis, 1 not mention the test used for the determination of Anti-HCV antibody, 1 evaluate the correlation between IL-12 /IL-13 levels and HCV infection in thalassemia, 1 mixing both alpha and beta thalassemia in one group, 1 mixing

beta thalassemia with sickle cell anaemia in one group and 1 presented HCV co-infection with HIV.

Data extraction

The data that were gathered from studies include: Title, first author name, year of publication, sample size, city of study, virus detection method, prevalence rate and HCV positive number.

Quality assessment

Studies quality assessed using Newcastle- Ottawa Scale (NOS) [23]. According to score, studies categorised in to 3 category, low (0-3), moderate (4-6), and high-quality (7-9).

Statistical analysis

The $\mathbf{I^2}$ statistic and Cochran Q were used to determine heterogeneity between the included studies [$\mathbf{(I^2 = (Q-df)/Q) \times 100\%]}$. [24]. No heterogeneity if I^2 equal to <25%; moderate heterogeneity I^2 = 25% - 50%; substantial heterogeneity I^2 =51% - 75%; and considerable heterogeneity I^2 > 75%. Heterogeneity considered significant if I^2 > 50% or Q statistic had P value of <0.1

Results

The search retrieved 23 studies, however, 5 studies were excluded because not fulfil the inclusion criteria. Fig.1 shows the flow diagram. Eighteen studies fulfilled the inclusion criteria which composed of 5451 patients with thalassemia were included in the systematic review. The year of data collection in the studies was between 2000 to 2020, Table 1.

The pooled HCV prevalence in beta thalassemia major was 20.49% (SD= 16.27; SEM= 3.47; Confidence interval 95% = 13.27, 27.71). There was a considerable heterogeneity between studies. In the ELISA method, the highest prevalence of HCV was 61.3% which observed in Baghdad province, while the lowest prevalence of 6.3% was observed in Mousel. However, using PCR, the highest prevalence rate of 61.5% was observed in Baghdad province, while lowest was observed in Mousel (1.6%).

Prevalence trend during the assessment period was varies from year to year. The highest rate was observed in 2006 (61.5%), while the lowest was observed for the year 2020. However, the prevalence trend was not with logical pattern. Of the 18 studies included, 8 studies (44.4%) regarded with high quality, Table 1.

Discussion

There are 3.7% to 6.5% of the Iraqi population at risk of getting HCV infection as they are thalassemic patients who need repeated blood transfusion. The present study indicated that HCV prevalence in beta thalassemia major was 20.49%. The studies from world different geographical areas reported varies prevalence rate of HCV in thalassemia. The variation influenced by method used for detection of HCV infection and the study time. The present study indicated considerable heterogeneity with varied prevalence from area to another. Previous studies in Iraq reported prevalence rate of HCV in thalassemia between 1.6% in Mousel to 61.5% in Baghdad. This heterogeneity may be attributed to differences between studies in relation to study design, study population, method of sampling, and the years of study performance.

Alwtaify and Hassan [25], 2000, Basrah, using ELISA method found that 9.5% of children with thalassemia compared to o.5% of the children in the control group in a prospective study that performed between November,1998 and May 1999. AlKubaisy et al [26], 2006, Baghdad, randomly collected 559 samples from children with thalassemia during 1998 reported a prevalence rate of 61.3% using ELISA methods. Additionally, they selected 78 samples randomly and tested by PCR which shows a rate of 61.5%. Rahman et al [27], 2011, Diyala, collected blood samples from thalassemia during the period from 1st January 1999 to 31st December 2000 and reported HCV prevalence rate of 26.4% using 3rd generation ELISA test and confirmatory immunoblot assay.

Aljubbori [28], 2012, Tikrit, collected 50 blood samples from thalassemic children during the period between March 2010 and February 2011. The Anti-HCV detected using 3rd generation ELISA and found prevalence rate of 10%, which was increased with age.

Albahadle et al [29], 2013, Baghdad, in a retrospective study during the period from May to September, 2011, a 206 reports of thalassemic children referred to Thalassemia and Hemoglobinopathy center in Ibn Albalady Teaching Hospital reported Anti-HCV antibody (3rd generation ELISA) prevalence rate of 19.9%. This illustrated a reduction in HCV prevalence in Baghdad province between 1998 [26] and 2011 [29].

Khaled [30], 2014, Mousel, in 480 blood samples collected from beta thalassemic major patients during the period from March and May 2012, found Anti-HCV antibody in 10.4% using 3rd generation ELISA, and viral particle positivity in 9.2% using PCR.

Tarish and Shakeer [31], 2014, Babylon, in a prospective study included 226 blood samples from children with beta thalassemia during the period between 1st of March to 1st of July found that HCV antibody positivity in 7.5% using 3rd generation ELISA. However, 5.2% were positive in PCR.

AlBadry [32], 2015, Thi-Qar, tested 394 blood samples from thalassemic patients during the period from September 2010 to July 2011, reported prevalence rate of 15.98% using 3rd generation ELISA.

Welli et al [33], 2015, Kirkuk, in a study included 254 multi-transfused thalassemia major patients found that 33.5% of tested blood samples were positive for Anti-HCV antibody, while the seropositivity was 1.3% in controls.

Hama and Sawa [34], 2017, Sulaimani, collected blood samples from 120 thalassemia major patients and found that 29.1% of them were positive for Anti-HCV by ELISA and confirmed by RIBA test.

Hussain and Jaber [35], 2018, Baghdad, cross-sectional study conducted and included 400 patients with beta thalassemia attending thalassemia center in Ibn Al-Balady hospital during the period from 1st of July to 31st of December, 2015. The prevalence rate of HCV was 26% using ELISA method and this seroprevalence was higher (26%) as compared to that performed in the same center and reported rate of 19.9% for the year 2011 [29].

Abed et al [36], 2018, Thi Qar, in a period from September 2016 to March 2017 they conducted a study which included 645 patients with thalassemia and found that 14.1% of tested samples were positive for Anti-HCV antibody using ELISA. Al-Khaffajy et al [37], 2019, Aqra, collected 117 blood samples from patients with thalassemia during the period between December 2015 and August 2016. Using Chemiluminescence Immunoassay, 11.1% of tested samples were positive HCV antibody.

Sadullah et al [38], 2020, Duhok, performed study that included 150 blood samples from patients with beta thalassemia and reported 35.3% detection rate of HCV antibodies. The seroprevalence was about 3 times higher than that reported for Aqra, Duhok [37], which may suggest an increase of HCV infection in thalassemic patients in Duhok governorate. Khudhair et al [39], 2020, Thi-Qar, tested 220 blood samples that were collected from patients with thalassemia during the period from August 2020 to October 2020 and found that 15.4% were positive for Anti-HCV antibodies using 3rd generation ELISA test.

Hasan et al [40], 2020, Sulaimani, in a cross-sectional study that included 459 patients with beta thalassemia major attending Sulaimani Thalassemia Centre during the period between January 2015 and June 2015, found that 13.9% were seropositive for Anti-HCV antibody using 3rd generation ELISA. The seropositive samples were confirmed by PCR. This finding indicated a reduction in HCV prevalence at year 2017 [34] as compared to that reported for 2020 [40].

Abdulla et al [41], 2020, Amara, in a study included 109 patients with beta thalassemia attending Thalassemia Centre in Amara city during the period from April 2017 to October 2017 reported a 27.5% prevalence rate of HCV using Enzyme Linked Fluorescent Assay (ELFA). Dawood etal [42], 2020, Mousel, conducted a study that included 752 patients with beta thalassemia attending Ibn-Alatheer Hospital Thalassemia Unit during the period between July 2018 and February 2020. Using ELISA, the Anti-HCV prevalence rate was 6.3% and only 1.6% was positive for HCV-RNA. The prevalence rate of HCV in Mousel reduced with time when findings of 2014 [30] compared to that of 2020 [42].

In Egypt, Mid-Delta study reported that 40% of thalassemic patients were infected with HCV [43]. Other study, during the period from January 2009 to January 2010 reported that 40.5% subjects were HCV antibody positive by ELISA and the Anti-HCV antibody positive cases 19.5% were positive for Anti-HCV antibody by recombinant immunoblot assay (RIBA) [44]. In addition, Mahmoud et al [45] performed study in Upper Egypt (from May 2014 to May 2015) reported Anti-HCV positive in 37.11% in children with thalassemia. However, high rate of 51% HCV infection was reported in thalassemic patients from Oman [46]. In Jordan Anti-HCV was detected in 32.8% of patients with beta thalassemia. [47].

In Pakistan, Hussein et al [48], 2008, found that 41.7% of beta thalassemic children were Anti-HCV positive by ELISA and the study cover two years Rawalpindi between October 2014 and November 2015 found Anti-HCV positivity in 38.75% by 3rd generation ELISA and confirmed by PCR. Descriptive cross-sectional study that included 379 children with thalassemia for a period from 1st January 2012 to 31st December 2014 shows Anti-HCV positive by ELISA was 32.45% [49]. Kiani et al [50], in a cross-sectional study that included 1253 thalassemia major patients (different country regions and ethnic groups) with history of multitransfusion during the period from July to December 2015 shows that HCV was positive in 21.7% by CLIA.

Yasmeen and Hasanain [51], recruited 350 thalassemia patients in Multan, Lahore, Peshawar and Karachi during period from December 2011 to December 2013 and screened for transfusion-transmitted infections. HCV infections found in 51% of thalassemia patients by immune chromatographic test (ICTs). Ehsan et al [52], in a systematic review and meta-analysis of 14 studies (3786 thalassemia patients) that performed during the period 2011 to 2019 found a prevalence rate of HCV of 26% (5.56% to 68.2%). In addition, Akhtar et al [53], in another systematic review and meta-analysis of 27 studies (5789 thalassemia patients) that performed during the period from 1995 to 2018 found that pooled HCV prevalence was 36.21% (95% CI :28.98-43.75%). The study indicated a considerable heterogeneity and prevalence range of 5.56% to 68.27%.

In Iran, Shamshirian et al [54], in a systematic review and meta-analysis of 37 studies (9185 thalassemia patients) that were performed between 1996 and 2015, reported that HCV pooled prevalence was 17% (95% CI: 14.5-19.8%) with a range of 0% to 45%. However, their finding indicated that HCV prevalence in thalassemia patients declined over time in Iran.

In India, Vidja et al [55], conducted cross-sectional study of 200 thalassemia patients during period from March to May 2010 and reported HCV seropositivity in 2% by ELISA. Jain et al [56], collected 96 blood samples from thalassemia patients during period from January 2007 to January 2009. Anti-HCV antibody detected in 25% by 4th generation ELISA and confirmed by western blot. Bhattacharyya et al [57], screened 300 thalassemic individuals during the period between 2011 and 2016 and found that 25% of patients were positive for Anti-HCV antibody by ELISA. Of the Anti-HCV positive samples, 65% of them were HCV RNA positive giving rate of 21.7% within the total tested samples. Gugnani et al [58], Punjab, collected a 126 blood samples from thalassemia patients during the period from

January to July 2018 and found that 13.4% were seropositive for HCV by ELISA test. In Western India, Mishra et al [59], reported anti-HCV seroprevalence of 51.1% in a study conducted on 196 beta thalassemia patients during 2015 by ELISA, while HCV-RNA positive in 33.7% by RT-PCR.

In Bangladesh, Bhuyan et al [60], Dhaka, reported HCV seroprevalence of 13.5% in beta thalassemia patients using ELISA in a study performed during period from August 2017 to February 2018.

The present study pooled seroprevalence of HCV in thalassemia patients was 20.49%, which was lower to that reported for Pakistan in two systematic review studies (36.1% and 26%)[52,53], while it was higher to that reported for Iran (17%) in a systematic review [54]. Other countries rate of HCV infection in thalassemia patients varies between countries and within countries area. In Egypt, the rate of HCV infection was with range of 19.5% to 40% [43-45], while in India the range was 2 to 51.1% [55-59].

To our knowledge, this is the first systematic review on the prevalence of HCV among beta thalassemia patients in Iraqi community which form the main strength of the study. The pooled HCV prevalence of 20.49% suggest the possibility on HCV endemicity in thalassemia patients who receive multiple transfusion as an important arm in cases management. Although, 3rd generation ELISA test that was used to detect Anti-HCV in most of the studies was with high sensitivity and specificity, however, there was a need to implement PCR as routine test for the detection of HCV-RNA in thalassemia patients.

The present study has limitations. As the study included in the review not cover all Iraqi governorate and thus limited country generalisation. Thus a national screening large-scale, incorporating a uniform well – planned program is warranted to overcome the variation in quality and scope of the studies. Some reports may be missed because they not published or there is no access to them.

Conclusions

HCV form the common transfusion-transmitted infections in beta thalassemia in Iraq. The overall of HCV in beta thalassemia in Iraq was 20.49%, but varies from area to others. Third generation ELISA test as screening test must be replaced by PCR and not restricted for positive ELISA as a confirmatory test. Relay on ELISA may not detect cases which were not seroconverted. National large-scale, well designed program that cover national and all governorates is warranted. Collaboration between medical colleges and regional health authorities is required and it was essential for national program success.

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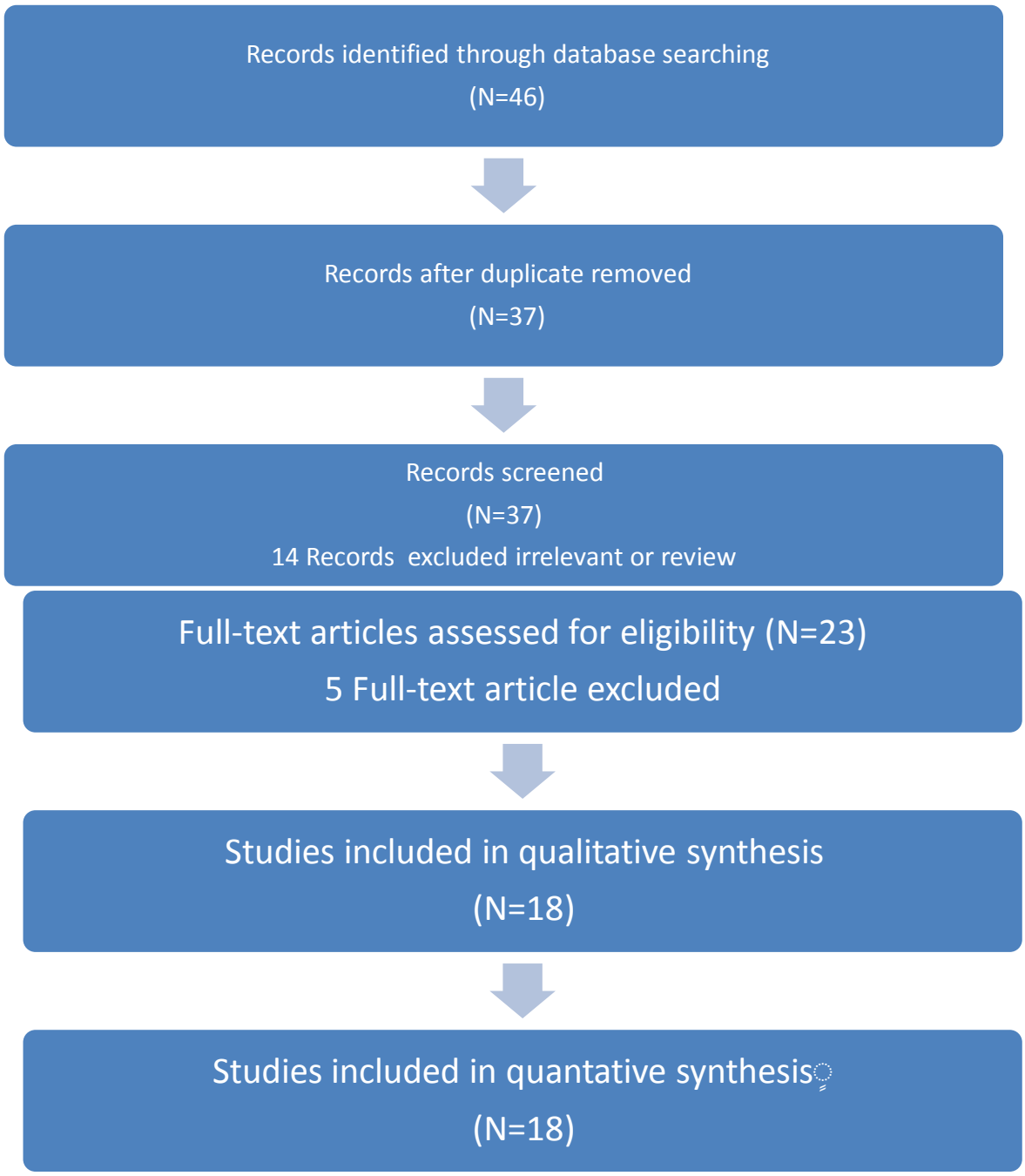

Fig.1. Flowchart of the study selection process

Table.1. Included studies summary

Author	Year	City	Sample size	Virus detection method	Number HCV positive	Study quality	Prevalence
Alwatify[17]	2000	Basrah	200	ELISA	19	High	9.5%
Alkubaisy [18]	2006	Baghdad	559 78	ELISA PCR	376 48	High	61.3% 61.5%
Rahman [19]	2011	Diyala	110	ELISA Immunoblot	29	High	26.4%
Aljuboori[20]	2012	Tikrit	50	ELISA	5	Medium	10%
Albahadle[21]	2013	Baghdad	206	ELISA	41	Medium	19.9%
Khaled [22]	2014	Mosul	480	PCR ELISA	44 50	High	9.2% 10.4%
Taresh [23]	2014	Babylon	226	ELISA PCR	17 12	High	7.5% 5.3%
Albadry [24]	2015	Thi-Qar	394	ELISA	63	Medium	15.98%
Welli [25]	2015	Kirkuk	254	ELISA	85	Medium	33.5%
Hama [26]	2017	Sulaimani	120	ELISA RIBA	35	High	29.1%
Hussein [27]	2018	Baghdad	400	ELISA	104	Medium	26%
Abed [28]	2018	Thi-Qar	645	ELISA	91	Medium	14.1%
Alkhaffaji [29]	2019	Aqra	117	CLIA	21	Medium	11.1%
Sadulla [30]	2020	Duhok	150	PCR Ab-HCV ?	53	Medium	35.3%
Khudhair [31]	2020	Thi-Qar	220	ELISA	34	Medium	15.4%
Hasan [32]	2020	Sulaimani	459	ELISA PCR	64	High	13.9
Abdulla [33]	2020	Amara	109	ELFA	30	Medium	27.5
Dawood [34]	2020	Mosul	752 752	ELISA PCR	48 12	High	6.3 1.6