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FULL PAPER

D-dimer as a diagnostic biomarker for pediatric/neonatal sepsis: A systematic review

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Diagnosis of sepsis is made based on clinical symptoms and laboratory findings, in which the clinical symptoms may be specific or nonspecific aim of D-dimer as a diagnostic biomarker for pediatric/neonatal sepsis. The researchers extracted all papers that had been published with the aim of examining pediatric and neonatal sepsis, and then they investigated them according to the inclusion and exclusion criteria, and finally included them. After the final conclusion and removal of the repeated papers, the results were reported using data frequency distribution table. In this study, in the initial search, 176 papers were found; after the initial and final screenings, the number reached 10 papers to be included in the SR stage. The total number of patients was 2075, on whom four studies had been done on one neonatal age group and six on children's age group. Furthermore, considering hospitalization in the ward, three studies had been done in NICU, 4 in PICU, and three studies in the pediatric ward. Moreover, the patients' mortality arranged from 0.9% to 52.7%. In all examined studies, it was observed that the patients with more severe clinical status or those who had died had higher levels of DD compared to other patients. In patients with more serious clinical status or those that had died, DD level was reported higher compared to the other patients. It seems that DD level can be used as a factor for disease diagnosis and prognosis of the patients.

KEYWORDS

D-Dimer; sepsis; pediatrics; neonatal.

Introduction

During the neonatal and pediatric periods, various diseases may threaten the individual life. These diseases may be congenital or have developed in the course of the person's life, with an example being infectious diseases [1]. As much as 26.5% of the global burden of disease and 25% of pediatric mortality in the world are related to the infections [2,3]. The infectious diseases lead to development of numerous complications including various psychological and physical disorders for the patient [4]. One of these infectious diseases is sepsis. Sepsis is the systematic reaction of the body to invade microorganisms including bacteria and fungi, and is one of the diseases which can lead to hospitalization in ICU [5]. Indeed, sepsis is a life-threatening associated disorder which occurs because of the irregular responses of the person to infection, and may cause septic shock for the patient, thereby confronting the patient with serious challenges and crises [6-8]. In this regard,

WHO has currently considered sepsis as an important threat for patient safety and health as well as the global health regarding prevention, diagnosis, and treatment of this disease, and thus has special emphasis on them [9].

In the US, annually about 300 per 100,000 cases of sepsis occur causing high economic burden for the patients [10]. Sepsis is very important in children and neonates, claiming 10% of mortalities related to children under five, which is highly notable [11]. Various factors affect the development of sepsis as well as prognosis of these patients. One of these factors is the clinical status of children and neonates. Underlying diseases as well as low birth weight are among the risk factors affecting poor prognosis of this disease [12,13]. Quantification of statistics and reports regarding the prevalence and the capacity to prevent sepsis can provide the significant implications for planning on the reduction of this disease. Through identifying the causes, factors, and its reduction methods, the huge healthcare costs as well as complications can be prevented that occur for these patients [14,15].

Diagnosis of sepsis is made based on clinical symptoms and laboratory findings, in which the clinical symptoms may be specific or nonspecific. The laboratory variables can provide more suitable findings for the earliest possible diagnosis of the disease as well as the appropriate solutions for improving and treating patients [16-18]. In patients suspected to have sepsis, various tests are checked each of which can provide specific clinical findings to the healthcare specialist. One of these tests is D-Dimer. DD is one of the products resulting from degradation of fibrin in the body which can be measured in the blood. With the increase of the fibrin lysis process in coagulation disorders, its value increases in the blood causing aggravation of disease. The DD elevation has been observed in patients with local or systemic identified infections, and it is associated with more severe disease, and also the need to provide more healthcare services. Likewise, this laboratory test is used for diagnosing venous thromboembolism, diffusing intravascular coagulation, and for screening patients [19-21].

Aim

Identifying suitable methods for diagnosing and treating diseases is one of the tasks and priorities of healthcare specialists, where systematic review can provide them with proper evidence. Accordingly, the present study was performed with the aim of D-dimer for diagnosis of pediatric/neonatal sepsis via a systematic review method on papers which have examined sepsis in children and neonates.

Materials and methods

Database search strategy

This study is a systematic review paper performed with the aim of D-dimer for diagnosis of pediatric/neonatal sepsis worldwide. The researchers performed search across domestic databases of Iran (SID, MagIran, IranMedex, and IranDoc) as well as international databases (Google scholar, Cochrane, Embase, ScienceDirect, Scopus, PubMed, and Web of Science) with no time constraint. The search was performed using Persian and English keywords according to the MESH system.

Selection of studies

The researchers extracted all papers that had been published with the aim of examining pediatric and neonatal sepsis, and then they investigated them according to the inclusion and exclusion criteria, and finally included them. The availability of full text of papers, measurement of DD in pediatric and neonatal groups, Persian or English papers, and the statistical population age being in the pediatric and neonatal age group were

considered as the inclusion criteria. On the other hand, case report, case series and meta-analyses, and the studies with unknown and repeated methodology, were excluded from the study. In this scrutiny, PICO criterion includes the following:
P: Pediatric/Neonatal diagnosis with sepsis;
I: Amount of DD in Pediatric/Neonatal diagnosis with sepsis;
C: Comparison of DD levels in healthy infants and children with sepsis;
O: Report on the Test value DD.

Paper selection and data extraction

In the first stage, all published papers were investigated, and then the papers which met the inclusion criteria were included. For data extraction, a checklist captured surname of the author, sample size, age range of patients, the country in which the research had been done, name of the place of hospitalization, mortality rate, age as well as the association of DD with clinical status of patients. The search was performed by two MSc students in nursing, and in case of any difference in the acquired results, the issue would be investigated by two pediatricians available in the research. Furthermore, all papers were introduced into EndNote software, and in the case of any similarity in them, the duplicate papers would be removed.

Statistical analysis

After the final conclusion and removal of repeated papers, the results were reported using data frequency distribution table.

Result

In this study, in the initial search, 176 papers were found; after the initial and final screenings, the number reached 10 papers to be included in the SR stage. The total number of patients was 2075, for whom four studies had been conducted on neonatal age group and six on children's age group. Besides, considering hospitalization in the ward, three studies had been done in NICU, 4 in PICU, and three studies in the pediatric ward. Moreover, mortality of patients arranged from 0.9% in the study by Zallocco *et al.* [22] in Italy to 52.7% in the study by Bay *et al.* [23] in Turkey. In all examined studies, it was observed that the patients with more severe clinical status or those who had died had higher levels of DD compared to other patients (Table 1). Figure 1 displays the flowchart of articles submitted to the SR stage.

TABLE 1 Status of articles entered in the SR stage

Authors	Years	N	Age	Country	Section name	type of study	Mortality rate	Gender and age	Relationship between D-dimer and neonatal clinical status
Jhang *et al.* [24]	2021	135	Neonatal	Korea	PICU	110 patients were in the survivor group and 25 in the non- survivor group.	18.7%	Out of the total 135 patients, 84 (62.2%) were male, out of whom 70 (63.6%) were in survivor and 14(56%) in non-survivor groups.	Out of the total 135 patients, 84 (62.2%) were male, out of whom 70 (63.6%) were in survivor and 14(56%) in non-survivor groups.
El-Shahat *et al.* [25]	2022	90	Neonatal	Egypt	NICU	45 neonates suffering from sepsis indicate group and 45 healthy neonates in the control group.	11%	In the case group, 23(51.1%) of patients were male, 22 (48.9%) were female, and their age range was 1-15. In the control group, 18(40%) of patients were male, 27(60%) were female, and their age range was 1-14 days.	In the case group, 23(51.1%) of patients were male, 22 (48.9%) were female, and their age range was 1-15. In the control group, 18(40%) of patients were male, 27(60%) were female, and their age range was 1-14 days.
Sharma *et al.* [26]	2018	50	Children	India	Pediatrics	50 patients were included who were assigned into the case and control groups.	10%	In both case and control groups, 32 (64%) were male and 18 (36%) were female. Also, M(SD) of the patients' age was 6.4(2.7) years, and all patients were within 1-10 years of age.	In both case and control groups, 32 (64%) were male and 18 (36%) were female. Likewise, M(SD) of the patients' age was 6.4(2.7) years, and all patients were within 1-10 years of age.
Li *et al.* [27]	2020	634	Children	China	PICU	476 patients were in the training group and 158 patients in the validation group.	25.4%	65.3% of patients were female and M(SD) of patients' age was 16.9(24.4). Besides, all patients were within the 1 month – 14 years age range.	65.3% of patients were female and M(SD) of patients' age was 16.9(24.4). Likewise, all patients were within the 1 month – 14 years age range.
Peker *et al.* [1][28]	2011	61	Infants	Turkey	NICU	40 patients were in the study group and 21 in the control group.	32.5%	In the study group, 26 neonatal patients were male and their mean age was 10.55(7.09) days; this value was 14 and 6.57(6.98) days in the control group, respectively.	In the study group, 26 neonatal patients were male and their mean age was 10.55(7.09) days; this value was 14 and 6.57(6.98) days in the control group, respectively.
Roman *et al.* [29]	1993	43	Newborns	Spain	NICU	In the control group, there were 20 neonates, in	-	The male gender in the control group was 10 neonates, in septic group 8 neonates, and in the shock group 5	The male gender in the control group was 10 neonates, in septic group 8 neonates, and in the shock

						the septic group 8 neonates, and in the shock group 15 neonates	neonates. The mean age of the neonates in the control group was 1.5 days, in septic group 1.7 days, and in shock group 1.5 days.	group 5 neonates. The mean age of the neonates in the control group was 1.5 days, in septic group 1.7 days, and in shock group 1.5 days.
Zallocco *et al.* [22]	2018	89	Children	Italy	outside the PICU	63 patients were Indian non-severe sepsis group and 26 patients in the severe sepsis group.	0.9%	In non-severe sepsis, there were 39 male patients with the mean age 8 (1-71) months; these values were 19 and 17 (2-111) months in the severe sepsis group, respectively.	In non-severe sepsis, there were 39 male patients with the mean age 8 (1-71) months; these values were 19 and 17 (2-111) months in the severe sepsis group, respectively.
Bay *et al.* [23]	2006	60	Children	Turkey	PICU	36 patients were in sepsis plus DIC group, 24 patients in the sepsis group, and 20 patients in the control group.	52.7%	In the sepsis plus DIC group, male gender was 22, in sepsis group 13, and in control group 5 patients. Besides, the age of patients in terms of months in the sepsis plus DIC, sepsis, and control groups was 21.08(27.4), 17.04(28.40), and 18.22(20.34), respectively.	In the sepsis plus DIC group, male gender was 22, in sepsis group 13, and in control group 5 patients. Furthermore, the age of patients in terms of months in the sepsis plus DIC, sepsis, and control groups was 21.08(27.4), 17.04(28.40), and 18.22(20.34), respectively.
Chen *et al.* [30]	2017	788	Children	China	PICU	438 patients were in the survival group, and 154 patients in the death group.	26.6	In the survival group, 78% had male gender and 74.8% were in the 1-month age group. Besides, in the death group, 85% were male and 74.8% were in the 1-month age group.	In the survival group, 78% had male gender and 74.8% were in the 1-month age group. Likewise, in the death group, 85% were male and 74.8% were in the 1-month age group.
Chen *et al.* [31]	2021	125	Pediatric	China	patients	69 patients were in nosocomial group, 56 patients in the non-nosocomial group, 94 patients in neutropenic group, and 31 patients in the non-neutropenic group.	-	In the nosocomial group, 60.7% of patients were male and their mean age was 5.8 (3.4-7.8) in terms of median (25th-75th percentile) (y). In the non-nosocomial group, 62.5% were male in the neutropenic group, 63.8% were male in the non-neutropenic group 54.8% were male.	In the nosocomial group, 60.7% of patients were male and their mean age was 5.8 (3.4-7.8) in terms of median (25^{th} -75^{th} percentile) (y). In the non-nosocomial group, 62.5% were male in the neutropenic group, 63.8% were male in the non-neutropenic group 54.8% were male.

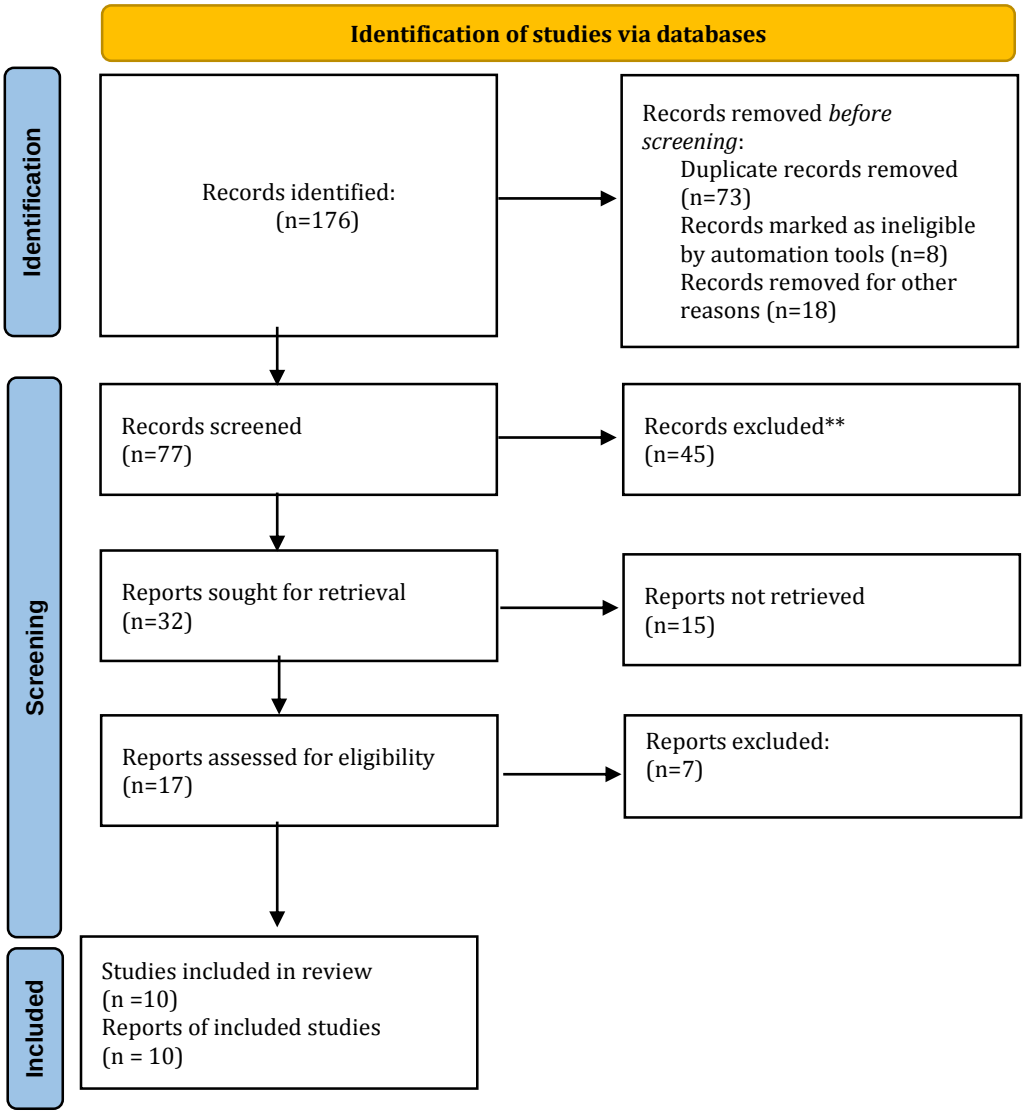

FIGURE 1 Flowcharts for systematic review

Discussion

Paying attention to the infectious patients, especially patients with a high prevalence, is one of the priorities of the medical staff [32]. The early diagnosis of the disease is the first and the most vital step in patients' management. Conducting tests is considered as the initial line of patient evaluation which provides complete information to the physicians [33,34]. For this reason, this study was performed as the primarily SR study on pediatric and neonatal age group suffering from sepsis worldwide.

Since no specific previous study had been done on the role of DD in sepsis diagnosis in pediatric and neonatal groups, the results of this study will be compared with other studies. According to the findings, DD level was significantly higher in patients with sepsis. In the meta-analysis by Yan *et al*., who examined the relationship between DD and joint infection, eight papers were analyzed in the patient group suffering from joint infection worldwide. According to the findings, DD can function as a suitable and practical method for joint infection especially in patients with no history of coagulation disorders [36]. In another meta-analysis study, Li *et al*. analyzed seven papers on the patients suffering from joint infection worldwide. They demonstrated that DD had higher sensitivity compared to plasma D-dimer. It was also found that the

sensitivity of serum DD in diagnosis of infection was higher than that of ESR and CRP tests [35]. This is in line with the results of this SR study in which DD has been higher in patients with sepsis.

Another study performed on the role of DD in characterizing the clinical status of patients was SR study by Vidali *et al.*, in which 16 papers published on COVID-19 patients had been included. They noted that DD status were evaluated in patients with COVID-19, and it was found that DD was higher in patients with COVID-19 and those with infection [37]. In the study by Shah et al. exploring the relationship between extent of DD and morbidity and mortality rate, it was found that in patients with positive DD in contrast to negative DD, comorbidity and mortality were two and four times higher, respectively [38]. In SR study by Varikasuvu et al., in which 13 papers had been included in the SR stage, it was observed that in patients with higher levels of DD, the risk of disease progression is higher [39]. In the present SR study, again DD was higher in patients with more severe clinical condition, which is in line with the results of the previous study.

It is recommended to use drug therapy in order to improve the status of laboratory variables in patients. In the study of Balavandi et al., It was revealed that the status of laboratory variables in heart patients has improved with drug therapy [40]. Likewise, in the study of Taheri et al., it was indicated that antibiotic therapy can improve sepsis in infants [41]. For this reason, it is recommended that medical interventions be performed in the field.

Since this study has been performed for the first time worldwide and has novelty, it is indeed the strong point of this study. Besides, this study has been performed through systematic review method; however, the meta-analysis statistical analyses have not been performed in it, which is a limitation. As such, it is suggested to perform meta-analysis study on D-dimer for diagnosis of Pediatric/Neonatal sepsis.

Conclusion

In patients with more serious clinical status or those that had died, DD level was reported higher compared to other patients. It seems that DD level can be used as a factor for disease diagnosis and prognosis of patients.

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