Research Paper: Sepsis Criteria and Revision in Toxicological Intensive Care Unit

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ABSTRACT

Background: Sepsis is one of the significant causes of mortality in hospitalized patients. This cross-sectional study was performed to determine the frequency of positive blood culture and assess sepsis criteria based on Third International Consensus Definitions (related to Sequential Organ Failure Assessment score) and clinical and paraclinical findings (i.e., on-admission leukocytosis, increased lactate level, and fever) in poisoned patients admitted to the Toxicological Intensive Care Unit (TICU).

Methods: Medical records of a total of 2000 poisoned patients admitted to the TICU of Loghman Hakim Hospital from 2016 to 2018 were assessed. Among them, 189 cases (9.45%) with suspected sepsis were considered eligible to be enrolled in the study.

Results: Of 189 cases, 146 (77.24%) had possible signs and symptoms of sepsis as well as SOFA score higher than two with positive blood culture in 81 cases (55%). The Mean $\pm$ SD serum level of lactate was 25.97 $\pm$ 16.32 on admission. The most common pathogen detected in blood culture was coagulase-negative Staphylococci in 35 (24.0%) out of 146 cases. Glasgow Coma Scale (GCS) less than 12, age older than 50 years, and bilirubin more than 1.2 mg/dL were found as independent predictors of sepsis on multivariate analysis.

Conclusion: Based on our findings, it is proposed that the sepsis definition should not be restricted to the guidelines. The patients' poisoning background and presence of many confounding factors, including poisoning-induced on-admission increased lactate levels, leukocytosis, and disturbed arterial blood gas provide a critical decision-making situation to confirm sepsis according to guidelines.

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1. Introduction

Sepsis is one of the life-threatening conditions caused by a dysregulated host response to infections [1-3]. According to the World Health Organization reports [4], the annual prevalence of sepsis has been reported to be around 30 million cases leading to 6 million deaths per year. This mortality rate is high and reported to be almost 30% in intensive care units (ICUs) [5, 6]. One of the basic cornerstones of goal-directed sepsis therapy is early control of infection. Early broad-spectrum antibacterial agents are recommended as empiric therapy for the first 24 to 48 h to improve the patient's survival rate [7, 8]. Since information on the pathogens and antibiotic susceptibility is not readily available to the treating physician, empiric therapy is initiated based on the clinician's experience, the location of the infection, and the pattern of microbial resistance in the admitting hospital [9-11].

Microorganism isolation plays an essential role in the diagnosis of sepsis and the specialist's decision to continue the prescribed antibiotic and modify the treatment [12]. The type of microorganism is determined by several methods, including blood culture, Polymerase Chain Reaction (PCR), matrix-assisted laser desorption/ionization time-of-flight, mass spectrometry, and in situ Fluorescence Hybridization (FISH). Among them, blood culture is cost-effective and readily available [2, 13, 14].

Sepsis management is mainly based on blood culture which has been recommended to be performed at least twice with both aerobic and anaerobic bottles before antimicrobial therapy: one is drawn percutaneously and one through each vascular access device (unless the device was inserted recently) to optimize identification of the causative organisms [15]. Bacteria are the most common causative microorganisms in sepsis and blood cultures are positive in about 30%-60% of cases [12, 16].

In Toxicological Intensive Care Units (TICUs), however, many poisoned patients refer with toxin-induced leukocytosis, increased lactate level, or lactate gap and fever [17-21]. The purpose of this study was to determine the frequency of positive blood culture and to assess sepsis criteria in poisoned patients admitted to TICU.

2. Materials and Methods

Definitions

According to the new Third International Consensus definitions for sepsis and septic shock (Sepsis-3), "sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection." The clinical criteria for sepsis include suspected or documented infection and an acute increase of two or more Sequential Organ Failure Assessment (SOFA) points as a proxy for organ dysfunction. Septic shock is defined by the clinical criteria of sepsis and vasopressor therapy needed to elevate mean arterial pressure ≥ 65 mm Hg and lactate >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation" [22]. The quick SOFA (qSOFA) score is measured simply based on clinical criteria without requiring laboratory tests which provides rapid evaluation of ICU patients and predicting mortality. However, in this study, we utilized SOFA score instead of qSOFA due to its high sensitivity in outcome prediction [2].

Study design

This cross-sectional study was conducted at TICU of Loghman-Hakim Hospital Poison Center, over three years from January 2016 to December 2018. This hospital is a unique teaching and referral center for poisoning treatment in Tehran with a nearly annual turnover of 15000 to 25000 Emergency Department (ED) visits. The study protocol was approved by the Ethics Review Committee in Research Deputy Department of Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Medical records of all patients (2000 cases) admitted to our TICU due to acute poisoning were evaluated. Poisoning was confirmed by lab tests in this center. Individuals who were clinically suspected to have sepsis during ICU stay (fever ($>38^{\circ}$ C) or hypothermia ($<36^{\circ}$ C), leukocytosis ($>12000/\text{mL}$) or leukopenia ($<4000/\text{mL}$), thrombocytopenia ($<100000/\text{mL}$), and/or hypotension (systolic blood pressure <90 mm Hg)) were enrolled from those with positive sepsis criteria and a SOFA score of 2 or more were studied. Blood culture was sent to all patients who were eligible to be enrolled in the study.

Patients were put on antibiotics if they were suspected to have aspiration or ventilator-associated pneumonia even before their culture results were ready. Some patients with immunodeficiency, diabetes mellitus, or poisoned with ethanol (which generally induces hypothermia) were considered to have pneumonia and

treated even if they had not developed fever. Albeit, those who had rhabdomyolysis, overdosed on medications/substances that induced hyperthermia and were on special antidotes that could precipitate hyperthermia (including atropine) were excluded from the cases who were considered to need antibiotic therapy.

A researcher-made questionnaire containing information on demographic data (age, sex, underlying disease), type of poisoning, the vital signs, lab tests (Complete Blood Count (CBC), Liver Function Test (LFT), bilirubin, urea, Creatinine (Cr), serum sodium and potassium, serum lactate level, erythrocyte sedimentation rate (ESR), C-reactive Protein (CRP), Blood Cultures (B/C), Tracheal Culture (T/C), Urine Culture (U/C)), and the type of antibiotic used before the onset of the fever according to the medical records was prepared and completed for all patients. FISH and PCR tests are not routine clinical practices in our centers due to economic limitations and blood culture is used as the gold standard in our country. The primary outcome was the frequency of negative blood culture in septic patients and the secondary outcome was hospital mortality.

Statistical analysis

The statistical analysis was performed in SPSS v. 16. The categorical variables were expressed as number (percentage) and numerical variables as Mean $\pm$ SD. The categorical variables were compared using the χ^2 test or Fisher exact test and other quantitative variables using the Student's *t* test or Mann-Whitney U test. To determine the independent predictors of sepsis, in addition to univariate analysis, multivariate logistic regression analysis was performed using a model consisted of variables that could potentially affect sepsis (age groups, sex, clinical and paraclinical parameters, and culture results). The Hosmer-Lemeshow goodness of fit test was utilized to assess model fit. A *P* value of ≤ 0.05 was considered significant and Odds Ratios (OR) were also presented with a 95% confidence interval (95% CI).

3. Results

Of 2000 cases, 189 were clinically suspected to be septic (had hypothermia or hyperthermia, leukopenia, leucocytosis, hypotension, and/or thrombocytopenia). Of them, 146 (77.24%) had possible signs and symptoms of sepsis, as well as SOFA, score higher than 2 who were finally enrolled and evaluated. A total of 101 (69.2%) were males. Their age range fell between 14 and 87 years with an Mean $\pm$ SD of 42 $\pm$ 18.6 years. Table

1 presents the patients' characteristics, poisoning, clinical and paraclinical factors at baseline and on the first day of ICU stay.

Opioids and or stimulants, as well as anticonvulsants and or antidepressants, were found as the most frequent types of poisoning in 39 and 35 patients, respectively. The underlying disease was only reported in four patients: stroke in one case, Parkinson disease in two, and bipolar disease in one. Antibiotics (mostly ceftriaxone-clindamycin in 16 cases (69.5%)) had been initiated in 23 patients before the onset of fever. The mortality rate was 32.2% (47 patients). The median of the SOFA score was 4.00 $\pm$ 1.78 (range; 2.00 to 12.00). Of these patients, 81 (55%) had positive blood culture and the remainder had negative culture results. The rate of sepsis in our TICU was 7.3% (146/2000).

Mean $\pm$ SD levels of lactate on admission (in 14 cases) was 25.97 (16.32). Fifty-four patients had leukocytosis (WBC > 12000/mL), four cases had leukopenia (WBC < 4000/mL), and 20 cases had thrombocytopenia (platelet < 100000/mL). Mean $\pm$ SD total bilirubin level was 1.40 (1.82) mg/dL.

Blood culture showed a sensitivity of 55.48%, specificity of 50%, the positive predictive value of 81.82%, the negative predictive value of 21.69%, and accuracy of 54.40% for the diagnosis of sepsis.

The most common bacteria isolated from blood, urine, and tracheal cultures were coagulase-negative Staphylococci in 35 cases (24.0%), *Escherichia coli* in 17 cases (11.6%), and *Staphylococcus aureus* in 36 cases (24.7%), respectively (Table 2). Moreover, coagulase-positive Staphylococci (10.3%) and *Acinetobacter* (9.6%) were found as the second and third most common pathogens in blood culture results, respectively.

Based on univariate analysis, Glasgow Coma Scale (GCS) less than 12, bilirubin more than 1.2 mg/dL, and positive urine culture were associated with higher frequency of sepsis. Age groups, including 36-40 years (OR=10.004, 95% CI:1.282-78.081, *P*<0.05), 51-55 years (OR=22.867, 95% CI:1.280-408.403, *P*<0.05) and >60 years (OR=6.683, 95% CI:1.07-41.75, *P*<0.05); GCS category, including 10 to 12 (OR=9.612, 95% CI: 1.345-68.670, *P*<0.05), 6 to 9 (OR=52.11, 95% CI:6.919-392.464, *P*<0.001) and <6 (OR=15.952, 95% CI:2.644-96.235, *P*<0.05), and bilirubin >1.2 mg/dL (OR=4.457, 95% CI:1.007-19.735, *P*<0.05) were found as independent predictors of sepsis on multivariate analysis (Table 3).

Table 1. Characteristics, poisoning, clinical, and paraclinical factors of 146 patients on admission and the first day of ICU stay

Variables		MeanSD (Range) / No. (%)
Characteristics	Age (y) Mean±SD (Range: 14-87)	42±18.6
Sex, No. (%)	Male	101 (69.2)
	Female	45 (30.8)
Poisoning, No. (%)	Opioid / stimulants	39 (26.7)
	Anticonvulsants / Antidepressants	35 (24.0)
	Opioid / Anticonvulsants	33 (22.6)
	Poison*	10 (6.8)
	Alcohol	2 (1.4)
	Others**	27 (18.5)
Antibiotics used before fever in 23 patients, No. (%)	Ceftriaxone-clindamycin	16 (69.56)
	Vancomycin	1 (4.35)
	Metronidazole	2 (8.69)
	Ampicillin/Sulbactam	1 (4.36)
	Meropenem / Vancomycin / Ciproflaxacin	3 (13.04)
Vital signs, Mean±SD (Range)	Temperature (°C)	36.98 (36.00-37.5)
	Heart rate (beats/min)	91.79± 16.93 (50-148)
	Respiratory rate (breaths/min)	17.39±7.18 (9-49)
	Systolic pressure (mm Hg)	115.39± 20.71 (60-190)
	Diastolic pressure (mm Hg)	71.79± 14.91 (39-134)
Paraclinical factor, Mean±SD (range)	White blood cell (×103/μL)	12301.39± 5529.54 (2800-34500)
	Red blood cell (×106/μL)	4642314.05± 743819.82 (2250000-6470000)
	Platelet (×103/μL)	214752.11±91291.63 (20000-523000)
	Aspartate transaminase (U/L)	207.28±709.76 (10-5750)
	Alanine transaminase (U/L)	184.24±643.93 (8-5160)
	Na (mEq/L)	138.80±4.09 (130-148)
	K (mEq/L)	4.15±0.72 (2.7-7.8)
	Lactate (mg/dl)***	25.97± 16.32 (12-71)
	Bilirubin-T (mg/dL)	1.40±1.82 (0.2-13.4)
	Creatinine (mg/dL)	1.45±0.85 (0.5-5.6)
	Erythrocyte sedimentation rate (mm/h)	18.17±19.03 (1-58)
	C-reactive protein (mg/L)	2026±24.08 (1-70)
	Partial thromboplastin time (s)	33.06±10.45 (10-97.7)
	International normalized ratio	1.35±0.76 (0.7-7.83)

* Organophosphorus, aluminum phosphide; ** Lithium, carbon monoxide, lidocaine, unknown.

*** Lactate level was measured in 14 patients

Table 2. Bacteria isolated from septic patients (146 patients)

Blood Culture		Urine Culture		Tracheal Culture	
Pathogen	No. (%)	Pathogen	No. (%)	Pathogen	No. (%)
Coagulase-negative staphylococci	35 (24.0)	E.coli	17 (11.6)	Staphylococcus aureus	36 (24.7)
Coagulase-positive staphylococci	15 (10.3)	Acinetobacter	10 (6.8)	Acinetobacter	19 (13.0)
Acinetobacter	14 (9.6)	Klebsiella	6 (4.1)	Klebsiella	18 (12.3)
Klebsiella	7 (4.8)	Staphylococcus aureus	3 (2.1)	Pseudomonas aeruginosa	4 (2.7)
Pseudomonas	4 (2.7)	Candida	3 (2.1)	E.coli	4 (2.7)
Enterobacter	2 (1.4)	Pseudomonas aeruginosa	2 (1.4)	Enterobacter	3 (2.1)
E.coli	2 (1.4)	Citrobacter	2 (1.4)	Streptococcus viridans	2 (1.4)
Streptococcus viridans	1 (0.7)	No culture	10 (6.8)	Citrobacter	1 (0.7)
Citrobacter	1 (0.7)	No growth	93 (63.7)	Proteus	1 (0.7)
No growth	65 (44.5)			No culture	11 (7.5)
P value	0.47	P value	0.21	No growth	47 (32.2)
				P value	0.13

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4. Discussion

Sepsis is one of the significant concerns in ICUs. The incidence of sepsis among patients admitted to ICUs varies from 6%-54% [23-25]. In one study in China, the incidence of severe sepsis was 37.3 cases per 100 ICU admissions [26]. In our TICU, the rate of sepsis was 7.3%. It should be noted that most patients in this study were young and had been hospitalized due to suicide or acute intoxication without underlying diseases. Additionally, based on the dominant microorganism in previous studies [17, 27, 28], these patients were treated by empiric antibiotic therapy at the onset of fever and infection.

The rate of positive blood culture for patients with severe sepsis was 58.5% in one study [15] and 53% in another [29] in the ICUs of public hospitals in France which is consistent with our results (more than 50%). However, Kumar and colleagues reported a lower frequency of positive blood cultures in their setting (34.2% versus 55.5%) [7].

Based on our results in culture-negative septic patients, the blood culture lacked the sensitivity to detect different types of micro-organisms possibly due to sampling error, insufficient volume for blood culture,

and slow-growing or fastidious bacteria [30]. Secondly, in some cases, culture-negative sepsis might have originated from nonbacterial pathogens like fungi or viruses. Fungi are the reason for approximately 25 to 30 per 100000 cases of healthcare-associated infections in ICUs [31, 32]. In some studies, viruses were more commonly detected than bacteria, accounting for higher than 25% of detections in adults and greater than 70% in children [33]. It is not a routine clinical practice in most ICUs, including ours, to test for viruses in pneumonia. Thirdly, previous antibiotic therapy could result in negative blood culture.

Since there was no significant difference between patients with positive- and negative-sepsis criteria in blood cultures, it seems that the competence of blood culture is significantly limited in these patients and confounding factors can sometimes lead to a misguided interpretation of microbiological results [34]. Remarkably, our patients' conditions differed from other general ICU patients because of poisoning-induced confounding factors, including multi-organ failure, hepatorenal dysfunction in rhabdomyolysis [35], and blood dyscrasia, including anemia and thrombocytopenia in some poisonings (e.g., linezolid, valproic acid, vancomycin, alcohol, carbamazepine, and digoxin toxicity) [36]. These parameters prompt difficulties in the

Table 3. Predictors of sepsis by univariate and multivariate logistic regression analyses

Demographics					
	Variable	Univariate OR (95%CI)	P	Multivariate OR (95%CI)	P
Age (Ref: 10-20 years)	21-25	0.727 (0.194-2.722)	0.636	0.470 (0.063-3.504)	0.462
	26-30	0.471 (0.132-1.679)	0.246	1.263 (0.126-12.695)	0.843
	31-35	1.600 (0.402-6.361)	0.504	10.472 (0.825-132.918)	0.070
	36-40	1.969 (0.671-5.781)	0.217	10.004 (1.282-78.081)	0.028
	41-45	2.000 (0.431-9.273)	0.376	8.695 (0.531-142.419)	0.129
	46-50	0.400 (0.070-2.277)	0.302	0.349 (0.016-7.478)	0.501
	51-55	2.800 (0.650-12.064)	0.167	22.867 (1.280-408.403)	0.033
	56-60	1.067 (0.240-4.740)	0.932	4.593 (0.318-66.264)	0.263
	>60	2.100 (0.755-5.843)	0.155	6.683 (1.070-41.750)	0.042
Clinical parameters	Sex (Ref: male)	0.618 (0.328-1.165)	0.137	2.951 (0.749-11.618)	0.122
	Fever (Ref: $\leq 38^{\circ}\text{C}$)	0.91 (0.507-1.634)	0.753	0.308 (0.083-1.145)	0.079
	Heart rate (Ref: ≤ 90 beats/min)	1.007 (0.547-1.853)	0.982	1.805 (0.616-5.290)	0.281
Paraclinical parameters	Respiratory rate (Ref: ≤ 20 breaths/min)	0.549 (0.097-3.117)	0.499	-	-
	Leukocytosis (Ref: $\leq 1200/\text{mL}$)	0.706 (0.384-1.296)	0.261	2.677 (0.863-8.308)	0.088
	Leukopenia (Ref: $\geq 4000/\text{mL}$)	4.1667 (0.477-36.399)	0.197	4.202 (0.212-83.245)	0.346
GCS (Ref: 15)	Thrombocytopenia (Ref: $\leq 100000/\text{mL}$)	1.506 (0.628-3.612)	0.359	0.353 (0.062-2.015)	0.241
	13-14	1.875 (0.465-7.566)	0.377	0.804 (0.112-5.791)	0.829
	10-12	4.687 (1.198-18.340)	0.026	9.612 (1.345-68.670)	0.024
	6-9	9.766 (2.860-33.341)	0.000	52.110 (6.919-392.464)	0.000
Creatinine (Ref: <1.2 mg/dL)	<6	7.589 (2.360-24.404)	0.001	15.952 (2.644-96.235)	0.003
	1.2-1.9	1.445 (0.721-2.897)	0.299	2.605 (0.757-8.959)	0.129
	2-3.4	1.889 (0.693-5.150)	0.214	2.650 (0.539-13.017)	0.230
	3.5-4.9	1.511 (0.205-11.119)	0.685	6.947 (0.000-1158203969.936)	0.841
Bilirubin (Ref: <1.2 mg/dL)	>5	2441162017.553 (0.000-.)	0.9990	4093953058.161 (0.000-.)	0.999
	1.2-1.9	3.845 (1.397-10.583)	0.009	4.457 (1.007-19.735)	0.049
	2-5.9	2.443 (0.763-7.821)	0.132	4.430 (.839-23.376)	0.079
	6-11.9	0.000 (0.000-.)	0.999	0.000 (0.000-.)	1.000
	>12	2192430173.098 (0.000-.)	1.000	2187255255.331 (0.000-.)	1.000
Cultures	Mean arterial pressure (Ref: <70 mm Hg)	0.978 (0.384-2.488)	0.962	0.680 (0.103-4.509)	0.689
	Blood culture (Ref: NO culture)	7269636188.413 (0.000-.)	0.996	-	-
	Urine culture (Ref: NO culture)	2.203 (1.201-4.043)	0.011	2.678 (0.935-7.669)	0.066
	Tracheal culture (Ref: NO culture)	1.153 (0.612-2.170)	0.660	0.796 (0.240-2.642)	0.710

^a Variables that were associated with sepsis on univariate or multivariate analyses are shown;International Journal of
Medical Toxicology & Forensic Medicine^b The Hosmer-Lemeshow test for goodness of fit for multivariate logistic regression model. (enter method): $\chi^2=6.56$, degrees of freedom=8, $P=0.58$.

determination of sepsis clinical and paraclinical criteria according to the guidelines.

In some studies, blood culture was compared with molecular methods and biomarkers eliciting that methodological improvements are required to replace or supplement traditional blood culture in the diagnosis of bacterial sepsis [37-41]. In recent years, studies of some septic patients have shown that the frequency of positive blood culture is often less than 50% [42]. However, we did have access to molecular methods, and accordingly, the sensitivity of blood culture in the determination of sepsis has risen to 55.48%.

One of the parameters for the diagnosis of septic shock is elevated serum lactate level particularly higher than 4 mmol/L is correlated with a mortality rate of about 30%. In a study in TICU by Talaie et al., it was reported that the lactate level of poisoned patients was high on admission (7.06 ± 5.29 mmol/L in non-survivors versus 3.01 ± 2.53 mmol/L in survivors ($P < 0.001$)) [20]. Erfantalab and colleagues studied 39 patients with aluminum phosphide poisoning in their TICU. They reported that blood lactate level was significantly higher in non-survivors on admission (within 8-16 hours post-ingestion) [43]. Moreover, alcohols (propylene glycol and methanol) have been associated with enhanced lactate levels, and lactate can be falsely increased in such cases [44, 45]. It appears that in poisoned patients measuring the lactate level cannot be used as a sepsis criterion due to its higher levels on admission.

One of the variables in multivariate modeling was age older than 50 years. Age is one of the risk factors of sepsis as the elderly population is more prone to infections due to the effects of aging on their immune system [46].

High bilirubin level was associated with increased risk of sepsis on multivariate analysis. Sepsis or septic shock affects the metabolism of hepatocytes towards the inflammatory response leading to liver dysfunction. The causes of hyperbilirubinemia in sepsis could be enumerated as follows: 1. Hepatic dysfunction; 2. Drug-induced or infection-related hemolysis; and 3. Cholestasis [47].

Leukocytosis and leukopenia were not significantly correlated to the development of sepsis in our cases. As this study was performed in TICU, the poisoning background of patients could lead to this high WBC count on admission, and mild to moderate leukocytosis was not an unusual paraclinical finding in our TICU [18].

Furthermore, the GCS category of 6 to 9 was featured as a significant predictor of sepsis. Alteration of consciousness on admission is an important clinical factor observed in our patients caused by poisoning.

Although fever is an important sign of infection in this study, it was not highlighted as a predictor of sepsis on logistic regression analysis.

Most pathogens isolated from blood culture in our study were Gram-positive bacteria, a finding in accordance with previous studies in developed countries [24, 48]. While in some studies performed in Singapore (2013) and China (2014), the majority of causative pathogens were Gram-negative bacteria [16, 26]. This difference may be due to skin colonization with *Staphylococcus aureus* in our IV drug user patients [49], more therapeutic manipulations compared to general ICUs (including more cases of insertion of intravenous catheters), and probable ward contamination with Gram-positive bacteria [50].

The limitations of this study are the possible variations in laboratory measurements from 2016 to 2018, antibiotic resistance, previous antibiotic therapy, small sample size, and lack of measuring the lactate level for all patients.

In conclusion, severe sepsis and septic shock are the main factors contributing to mortality in ICUs. In other words, our patients' poisoning background and the presence of many confounding factors on-admission lead to difficulties in the diagnosis of sepsis. It seems that the sepsis definition is required to be revised in this ward and should not be restricted to the guidelines.

Ethical Considerations

Compliance with ethical guidelines

The study protocol was approved by the Ethics Review Committee in Research Deputy Department of Shahid Beheshti University of Medical Sciences, Tehran, Iran (Code: IR.SBMU.RETECH.REC.1397.1040).

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Author's contributions

Conceptualization, data curation, review, and editing: Haleh Talaie; Writing and data collection: Maryam Nazari; Data analysis: Habib Emami.

Conflict of interest

The authors declared no conflict of interest.

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