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Mortality Predictors in Sepsis: A Retrospective Study

Sepsiste Mortalite Prediktörleri: Retrospektif Bir Çalışma

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ABSTRACT *Objective:* In our study we aimed to assess the specificity and sensitivity of three predictors of mortality in patients with sepsis: the presence of infection-causing microorganisms, the severity of disease classifications, and biomarkers.
Materials and Methods: We retrospectively analyzed the files of 76 patients. All patients were over the age of 18, diagnosed with sepsis, and admitted, treated, and followed up in our hospital's Reanimation Unit between 01/01/2017 - 01/01/2018. Patients' demographic data, treatments in the ICU, causes and durations, biochemical analyses, 24 hour acute physiology and chronic health evaluation (APACHE II) scores, sequential organ failure assessment (SOFA) scores, and microorganisms detected through culture analysis were analyzed in terms of their specificity and sensitivity in predicting mortality and morbidity.
Results: Of the patients analyzed, 46.05% were women and 53.95% were men. The average age was 62.67±18.1 years, and the mortality rate was 51.31%. While sepsis developed post-operatively in 60.53% of patients, 39.47% of patients developed sepsis due to internal medical pathology. The average duration of treatment was 35±43.7 days. The most common infection-causing pathogen was Klebsiella pneumoniae, followed by Staphylococcus aureus. In terms of fungal infections, Candida spp. was found to be the most common. In the first 24 hours of treatment, high SOFA, APACHE II, procalcitonin (PCT) values, and infection with Enterococcus faecalis were all found to be independent risk factors for mortality ($p<0.05$).
Conclusion: In patients with sepsis, severity of disease classifications and Enterococcus faecalis infection are independent risk factors of high mortality rates. They should be considered when evaluating patients.
Keywords: Sepsis, biomarkers, APACHE II-SOFA, mortality

ÖZ *Amaç:* Çalışmamızda, sepsis tanılı hastalarda enfeksiyona sebep olan mikroorganizmaların, hastalık ciddiyet skorlamalarının ve biyobelirteçlerin mortalite prediktörü olarak özgüllük ve duyarlılıklarını tespit etmeyi amaçladık.
*Gereç ve Yöntem:*Çalışmamızda hastanemiz Reanimasyon Ünitesinde 01.01.2017 - 01.01.2018 tarihleri arasında sepsis tanısı alarak takip ve tedavi edilen 18 yaşından büyük 76 hastanın kayıtları retrospektif olarak incelendi. Hastaların demografik verileri, yoğun bakım ünitesine yatış tedavileri, nedenleri ve süreleri, biyokimyasal analizleri, ilk yirmidört saatinde hesaplanan Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi Skoru (APACHE II) ve Ardışık Organ Yetmezliği Değerlendirme Skoru(SOFA) ile kültür analizi sonucunda üreyen mikroorganizmalar mortalite ve morbidite prediksiyonu açısından duyarlılık ve özgüllükleri kıyaslandı.
Bulgular: Hastaların %46,05'i kadın,%53,95'i erkek, yaş ortalamaları 62,67±18,1 yıl, mortalite oranı %51,31 olarak tespit edildi. Hastaların %60,53 cerrahi operasyon sonrası, %39,47 dahili nedenler ile sepsis tanısı almış olup ortalama tedavi süresi 35±43,7 gündü. Enfeksiyona neden olan etken en sık Klebsiella pneumoniae, ikinci sıklıkta Staphylococcus aureus, fungal etken olarak ise Candida spp. olarak bulundu. Tedavilerin ilk 24 saatinde ölçülen yüksek SOFA, APACHE II skorlarının, PCT değeri ve Enterococcus faecalis enfeksiyonu mortalite için bağımsız birer risk faktörü olarak belirlendi ($p<0,05$).
Sonuç: Sepsisli hastalarda mortalite prediksiyonunda, skorlama sistemlerinin yanında Enterococcus faecalis enfeksiyonun da bağımsız bir risk faktörü olması yüksek mortalite açısından dikkate alınmalıdır.
Anahtar Kelimeler: Sepsis, biyobelirteçler, APACHE II-SOFA, mortalite

Introduction

Sepsis is syndrome characterised by an uncontrolled inflammatory response to infection that leads to physiological, biological, and biochemical abnormalities (1). Early diagnosis and appropriate treatment have a positive effect on prognosis. If early diagnosis and appropriate treatment are not carried out, the initial illness may progress to conditions such as septic shock and multiple organ failure, leading to a high mortality rates (2).

To predict the course of sepsis, it is important to know the organism that causes it. The most common pathogens causing sepsis are bacteria; however, viruses, fungi, and parasites can also lead to sepsis. The 2009 European Prevalence of Infection in Intensive Care (EPIC II) study found Gram (-) microorganisms to be the more common cause of sepsis (62.2% vs 46.8%) (3). Alongside this, other studies have found that the incidence of Gram (+) microorganisms is increasing. Multi-center studies in recent years have shown that, in Turkey, the most commonly isolated pathogens are Gram (-) bacteria, while the second most common are Gram (+) bacteria (4). Following these, fungi and viruses are the most common pathogens (4). Nevertheless, sufficient epidemiological data on sepsis is as of yet unavailable in Turkey.

Prognostic insight into patients diagnosed with sepsis can be provided by evaluating basic biological parameters alongside various biomarkers and early disease severity classification scoring (5). Most common are the APACHE II and SOFA classification systems used in the ICU. Internationally, varying results have been reported in terms of the effectiveness of these systems in predicting mortality. For this reason, these classification systems are used in combination with other biomarkers to determine prognosis. While a wide range of biomarkers have been studied in the past decade for their use in patients with sepsis, only a few of these have proven to be useful clinically. C-reactive protein (CRP) and procalcitonin (PCT) are the most widely used and well studied of these biomarkers. However, neither of these factors has been found to be sufficiently reliable in isolation.

In our study, patients diagnosed with sepsis and subsequently treated and followed up in the Reanimation Unit were evaluated in terms of causative microorganisms, APACHE II and SOFA severity of disease classification scores, and biomarkers such as CRP and PCT. We aimed to investigate these parameters' sensitivity and specificity in predicting mortality.

Materials and Methods

This study was carried out in the Anaesthesiology and Reanimation Unit of XXXXXXXXXXXX, with approval from the hospital ethics committee garnered on 17/08/2017 under number 2017/603. Seventy-six patients admitted and treated in the Reanimation Unit for sepsis between 01/01/2017 and 01/01/2018 were retrospectively included in the study through access to and evaluation of their patient files and electronically stored data.

Patients diagnosed with sepsis based on the Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2016 Sepsis-3 diagnosis criteria were included after an evaluation of patients' files (6). Patients that were younger than 18 years of age, pregnant, undergoing immunosuppressive therapy, were HIV (+), or had any diagnosed organ failure were excluded from the study.

Patients included in the study were evaluated with respect to their demographic data, reason for admission to the intensive care unit (either surgical or internal pathology), first day PCT, CRP, and white blood cell (WBC) values, and severity of disease classification scores (APACHE II and SOFA). Furthermore, growth of microorganisms, microorganism locus (e.g. tracheal aspirate or blood), need for mechanical ventilation, inotropic and vasoactive agents used, need for renal replacement, and duration of inpatient treatment in the Intensive Care Unit were each evaluated and recorded.

Recorded parameters were analyzed in terms of either their independent or combined value in predicting mortality in patients with sepsis. Results were evaluated for their sensitivity and specificity in predicting mortality in patients with sepsis and septic shock.

Statistical Analysis

Statistical analysis was carried out using NCSS (Number Cruncher Statistical System) 2007 Statistical Software Package (Utah, USA) in combination with the STATA 12 Statistics Package.

Analysis of data was carried out using descriptive statistical methods (average ± standard deviation, median [minimum - maximum], interquartile range). Pairs of normally distributed variables were compared using the independent t-test, while non-normally distributed pairs were analyzed using the Mann-Whitney U test. Qualitative variables were evaluated using the Chi-squared and Fisher's exact test.

Odds ratios (OR) were calculated using a 95% confidence interval (95% CI). The factors affecting development of mortality were evaluated using logistic regression analysis.

The predicted results of the regression analysis were obtained using two separate software packages, and statistical significance was defined as $p<0.05$.

To determine APACHE and SOFA classifications' respective predictive values in terms of mortality, AUROC (Area Under Receiver Operating Characteristic) curve analysis was carried out and areas underneath the AUROC curve were evaluated. The larger test's area, which was located underneath the AUROC curve, was determined to be a parameter of greater value in predicting mortality.

Results

Seventy-six patients diagnosed with and treated for sepsis in the Anaesthesiology and Reanimation Unit of XXXXXXXXXX between 01/01/2017 and 01/01/2018 were analyzed in terms of their infectious agents causing sepsis, biomarkers, severity of disease classification scores, and the treatments they underwent. Each parameter's respective relationship to mortality was then evaluated.

Of the 76 patients included, 35 (46.05%) were women and 41 (53.95%) were men. The average age was 62.67±18.1 (20 - 93). Values were calculated as (average±SD (min-max)) years. Of these patients, 60.53% were admitted to our ICU post-operatively, while 39.47% were admitted due to internal medical reasons (respiratory failure, pneumonia). Patients with sepsis underwent inpatient treatment for an average of 35±43,7 days (1 - 271). Of these patients, 51.31% died, while 48.68% recovered and were discharged. Table 1 shows the demographic data, inpatient treatment durations, and mortality rates of the patients.

Of the patients included in the study, median (min - max) SOFA score in the first 24 hours was 8 (2 - 17), and median (min - max) APACHE II score was 20 (5 - 38). The average CRP value was 196.2±166.3 (0.74-1242.2) mg/dl, WBC average was 18.04±12.6 (1.2-69.8), and average PCT value was 17.8±30 (0.06-120) ng/ml (Table 2,3).

Table 1. Patients' demographic data, inpatient treatment durations, and mortality rates

Sex (female/male) n (%)	35/41 (%46.05/%53.95)
Age (years) average ± SD (min - max)	62.67±18.1 (20-93)
Inpatient treatment duration (days) average ± SD (min - max)	35±43.7 (1-271)
Mortality n (%)	39 (%51.31)

The microorganism responsible for infection was isolated in 96.05% of the 76 patients included in the study (n:73). Disease-causing microorganisms were most commonly isolated from blood (30.26%, n:23), followed by deep tracheal aspirate (DTA) (27.63%, n:21). Our analysis found no significant correlation between patients' infection loci and mortality.

Microorganisms causing infection were mostly Gram (-) (59.22%), followed by Gram (+) (33.76%) and fungal infections (7.89%). Klebsiella pneumoniae (K. pneumoniae) was the most commonly isolated bacterium (n:14, 18.42%), followed by Staphylococcus aureus (S. aureus) (n:11, 14.47%). Candida spp. was the predominant microorganism in fungal infections (n:6, 7.89%).

Our analysis of the effect of isolated microorganisms on mortality showed that Enterococcus faecalis (E. faecalis) was isolated from 19.51% of 39 patients that died. Of the 9 patients whose cultures exhibited growth of E. faecalis, 8 of them (88.8%) died. Statistical analysis showed that the presence of E. faecalis was positively correlated with

Table 2. Patients' admission APACHE II scores, SOFA scores, CRP, WBC, and PCT values

	n	Average±SD	Median (min - max)
CRP mg/dL	76	196.2±166.3	176 (0.74-1242.2)
WBC x10³/mm³	76	18.0±12.6	15 (1.2-69.8)
PCT ng/mL	76	17.8±30.0	4 (0.06-120)
SOFA	76	8±3	8 (2-17)
APACHE II	76	20±8	20 (5-38)

Table 3. Distribution of isolated microorganisms

	n	%
Klebsiella pneumoniae	14	18.42
Staphylococcus aureus	11	14.47
Acinetobacter	10	13.16
Escherichia coli	10	13.16
Enterococcus faecalis	9	11.39
Pseudomonas aeruginosa	8	10.53
Candida ssp.	6	7.89
Staphylococcusepidermidis	5	6.58
Haemophilus influenza	2	2.63
Streptococcusanginosus	1	1.32
Stenotrophomonas maltophilia	1	1.32

mortality, and E. faecalis isolation was associated with an increased risk of mortality (p=0.017). Of the other isolated microorganisms, none were significantly associated with mortality rates (p>0.05) (Table 4)

Duration of treatment for included patients and laboratory biomarkers measured during inpatient treatment (CRP, WBC, PCT) were examined for their relationship with mortality (Table 6). Duration of inpatient treatment, as well as first 24-hour WBC and CRP values, was not found to be significantly related with mortality (p>0.05). High PCT values were shown to be independent risk factors for mortality (p=0.0078).

SOFA and APACHE II scores recorded within the first 24 hours of treatment were each found to be significantly positively correlated with mortality (p=0.006, p=0.0005, respectively) (Table 5).

Of the patients who died, 94.87% (n:37) received some form of inotropic treatment, 48.72% (n:19) received renal replacement therapy (RRT), and 97.44% (n:38) received mechanical ventilation (MV) support. Analysis showed all of the aforementioned therapies (inotrope, RRT, and MV) to be significantly positively correlated with mortality rates (p=0.000, p=0.003, p=0.04, respectively).

To compare the predictive value of SOFA and APACHE scores with respect to mortality, AUROC (Area Under Receiver Operating Characteristic) curve analysis was carried out and the areas under the curve compared. The area under the AUROC curve was found to be larger in SOFA (area under ROC curve = 0.7449) compared to APACHE II (area under ROC curve = 0.733). SOFA was determined to be a more successful parameter with regard to its value in predicting mortality (Graph 1, 2).

Logistic regression analysis was carried out for each of the variables that showed a positive correlation with mortality (PCT, age, SOFA, APACHE II, inotropic therapy, RRT, MV, and E. faecalis growth). Age (p<0.01), E. faecalis growth (p<0.01) and inotropic therapy (p<0.01) were found to be the variables most valuable in predicting mortality (Table 6).

Table 4. Microorganisms' relationship with mortality

Microorganism	Growth	Survival n=37		Mortality n=39		p
		n	%	n	%	
Enterococcus faecalis	(-)	36	97.37	31	80.49	0.017
	(+)	1	2.63	8	19.51	
Staphylococcus aureus	(-)	30	81.08	35	89.74	0.441
	(+)	7	18.91	4	10.25	
Acinetobacter	(-)	32	86.84	34	87.80	0.597
	(+)	5	13.16	5	12.20	
Pseudomonas aeruginosa	(-)	33	89.47	35	90.24	0.614
	(+)	4	10.53	4	9.76	
Haemophilus influenza	(-)	36	97.37	38	97.56	0.74
	(+)	1	2.63	1	2.44	
Escherichia coli	(-)	30	81.58	36	92.68	0.134
	(+)	7	18.42	3	7.32	
Klebsiella pneumoniae	(-)	32	86.84	30	78.05	0.219
	(+)	5	13.16	9	21.95	
Streptococcus anginosus	(-)	36	97.37	39	100.00	0.487
	(+)	1	2.63	0	0.00	
Candida ssp.	(-)	35	94.74	35	90.24	0.363
	(+)	2	5.26	4	9.76	
Stenotrophomonas maltophilia	(-)	36	97.37	39	100.00	0.487
	(+)	1	2.63	0	0.00	

The p values displayed are the results of Fisher's exact test. p<0.05 was set as the threshold for statistical significance.

Discussion

Sepsis is an uncontrolled inflammatory response that can lead to organ failure. It is an increasingly common syndrome that affects millions of people every year (7). Due to sepsis' high mortality and morbidity, the prompt diagnosis and appropriate provision of treatment according to the severity and prognosis of the disease is of utmost importance. In order to provide an early prediction of the prognosis of septic patients, we investigated proven infectious agents, biomarkers (CRP, WBC, and PCT), and the severity of disease classification scores (SOFA, APACHE II). Each factor was analyzed for their relationship with mortality to assess their sensitivity, specificity, and predictive value. Furthermore, patients' demographic data as well as treatments (inotropic therapy, RRT, MV support) were analyzed with respect to mortality.

A retrospective study involving 6,621,559 patients diagnosed with sepsis found that yearly sepsis incidence was 3/1000 for the general population but 26.2/1000 for patients 85 years and older (7). This study determined that aging was an independent risk factor for both development of sepsis and death due to sepsis (7). In the same study, total mortality rates for sepsis were found to be 28.2%, while this figure was 38.4% for patients 85 years and older (7). A different study found that sepsis mortality rates were 24.4%, with mortality steadily increasing with age (8). Patients under 65 years old had a 17.7% chance of dying if diagnosed with sepsis, while patients 65 years and older had a 27.7% mortality rate (8). Logistic regression analysis in the same study showed that being over the age of 65 independently increased risk of mortality due to sepsis by a factor of 2.26 (8). In our study, patients included had a mortality rate of 51.31%. When patients' mortality rates were compared with respect to their age, 20 - 34 year olds, 35 - 49 year olds, 50 - 64 year olds, 65 - 74 year olds, and patients aged 75 and older were found to have mortality rates of 25%, 37.5%, 47.4%, 57.2%, and 65%, respectively. Thus, sepsis incidence and mortality were found to be positively correlated with advancing age.

Two important prognostic factors in sepsis are the infection locus and the causative microorganism. In several different publications, the most common infection locus was found to be the respiratory tract, followed by the intra-abdominal region, and subsequently the urinary system, blood, and soft tissues (4, 9 - 12). In terms of microbiological

Table 5. Duration of treatment, severity of disease classification scores and biomarkers' relationship with mortality

	Mortality	Average ± SD	Median	(IQR)	p
Duration of Treatment (days)	(-)	34.32±41.49	14	(6.75-47.50)	0.482
	(+)	35.69±46.27	20	(6.5-46.5)	
CRP (mg/dl)	(-)	174.77±110.41	177.65	(77.88 - 235.23)	0.479
	(+)	216.57±205.37	179.4	(91-301.63)	
WBC ($x10^3/mm^3$)	(-)	15.43±10.61	13.65	(7.83-20.4)	0.057
	(+)	20.52±13.92	17.6	(11.25-25.5)	
PCT (ng/mL)	(-)	11.44±24.03	2.4	(1.06-5.88)	0.0078
	(+)	24.47±36.80	10.52	(1.96-29.35)	
SOFA	(-)	6.19±2.96	6	(3.75-8)	0.0006
	(+)	9.17±3.91	9	(7-12)	
APACHE II	(-)	18.35±6.02	18	(14-22)	0.0005
	(+)	24.43±7.45	27	(19-30.5)	

The p values displayed are the results of the Mann-Whitney U test. p<0.05 was set as the threshold for statistical significance.

Table 6. Logistic regression analysis of factors correlating with mortality

Variable	PCT	SOFA	APACHE II	Inotrope	RRT	MV	Age	*E. faecalis*
Mortality	0.0244*	0.0740	0.00648	3.088***	1.029	0.232	0.0618***	2.274***
	(0.0146)	(0.125)	(0.0564)	(1.053)	(0.711)	(1.469)	(0.0217)	(0.813)

*** p<0.01, ** p<0.05, * p<0.1

environment, bacteria were most often isolated on blood culture (4, 9 - 12). In our patients, the most common infection locus was the respiratory system, followed by the digestive system and the urinary system, respectively. Microbiological infectious agents were most frequently isolated from blood samples (30.26%), followed by DTA, and finally from soft tissue / lesion cultures. In our study, no significant association was found between infection locus and mortality.

The specific causative microorganisms associated with sepsis were not found to be of importance for prognosis. Other publications have identified the relevant infectious agents, which include, in order of commonality, Gram (-) bacilli, Gram (+) cocci, and fungal agents (4, 10, 11). For specific microorganisms, the most common include, in order of frequency, Acinetobacter spp., Pseudomonas, spp., Klebsiella spp., Staph. aureus, Enterococcus spp., E. coli, and Candida spp. (4, 10, 11). Though patients with sepsis are most commonly infected with Gram (-) bacteria, in recent years the increase of nosocomial infections has caused Gram (+) related bacterial sepsis to occur increasingly often (9). In our study, 59.22% of cases were associated with Gram (-) bacteria, 33.76% with Gram (+) bacteria, and 7.89% with fungal infections. Examining the incidence of microorganisms revealed the most common to be K. pneumoniae (18.42%), followed by Staph. aureus (14.47%), Acinetobacter spp. (13.14%), E. coli (13.16%), E. faecalis (11.39%), P. aureginosa (10.53%), and Candida spp. (7.89%). While Gram (-) bacteria were observed more frequently in our study, the distribution of infectious agents was found to be different from those described in the literature. This may be caused by the variation in flora between our ICU and centers where other studies were conducted.

In a study assessing mortality rates in patients with sepsis according to microorganisms, 28-day mortality rates were found to be 40.5% in patients infected with Gram (-) bacilli, 42.9% for Gram (+) cocci, and 52.4% for sepsis associated with fungal infections (108). In the last ten years, the third most common species isolated in nosocomial infections is Enterococcus spp., which has appeared with increasing frequency (13). A retrospective study on mortality rates of 196 patients with growth of Enterococcus spp. on blood cultures found that inappropriate use of antibiotics was an independent risk factor associated with mortality, while mortality rates were 26% in cases with appropriate antibiotic therapy (14). In a prospective study analyzing 398 patients infected with Enterococcus spp., 14-day mortality rates were found to be 19% and vancomycin resistance was found to be an independent risk factor for mortality. While assessing infectious agents' relationship with mortality in our study, E. faecalis was found to be associated with a higher risk of mortality compared to other microorganisms that we isolated. Presence of Enterococcus spp. was also found to be an independent risk factor for mortality.

In studies carried out on patients diagnosed with sepsis, promptly measured PCT levels are known to be of predictive value for mortality rates (16, 17). Another study analyzing response to antibiotic therapy found that CRP is a potentially preferable biomarker over PCT. Despite this, PCT has been determined to be of greater prognostic value than CRP in evaluating organ failure and mortality risk in patients with sepsis (18). In our study, patients' PCT values as measured in the first 24 hours were found to be positively correlated with mortality. While high PCT values were found to be independent risk factors for mortality, we found no such relationship for high CRP values.

Across the globe, the most commonly used scoring systems in ICUs are SOFA and APACHE II. These systems contain multiple parameters and are not specific to sepsis. Various studies have investigated whether they can predict mortality in isolation or when combined. In one prospective study, inpatients with a SOFA score ≥11 in the first 24 hours were found to have higher mortality rates while, in 48 hourly followups, SOFA scores ≥50% were similarly associated with high mortality (19). Consequently, SOFA scores have been found to be valuable parameters in determining mortality risk (19). In a study conducted by Fang et al., patients were divided into three groups: all infected patients, patients without preexisting organ dysfunction, and patients with existing organ dysfunction. In terms of predicting 21 day mortality, SOFA scores of 2 and more were found to be 94.2%, 91%, and 97.6% sensitive, respectively, while specificity was 16.9%, 21.9%, and 7.2%, respectively (20).

A retrospective study of 415 patients undergoing treatment in the ICU assessed the relationship between APACHE II scores and mortality. It found that APACHE II scores of 27 and over were associated with increased mortality (21). In our study, both SOFA and APACHE II scores as recorded in the first 24 hours were found to be significantly associated with mortality. Mortality in patients with high SOFA and APACHE II scores as calculated at diagnosis had significantly higher mortality rates. In AUROC analysis, which was carried out in order to assess these scoring systems'

sensitivity and specificity in predicting mortality, the SOFA AUROC curve value was 0.7449 and the APACHE II AUROC curve value was 0.733. According to these results, the SOFA scoring system was a better parameter in terms of its value as a predictor of mortality.

Study Limitations

The study was subject to several limitations due to a number of factors: the patient population was relatively small, the patients' reasons for admissions were varied, it was carried out retrospectively, and it was a single center study. The study's single-center nature means that the variance in microbial flora between centers may have had an effect on the data.

Conclusion

The locus of the infection leading to sepsis was found not to have a significant effect on mortality. However, the infective microorganism was found to potentially increase mortality. Specifically, Enterococcus spp. infection was found to be an independent risk factor for infection. Furthermore, in place of CRP or WBC values, PCT was found to be a more specific biomarker in terms of predicting patients' prognosis.

Meetings:The study was presented in 22th İnternational İntensive Care Symposıum, 3-4 May 2019- İstanbul as an oral presentation(OP-248).

Ethics

Ethical Commite Approval: University of Health Sciences, Bağcılar Training and Research Hospital Training and Research Hospital ethics committee garnered on 17/08/2017 under number 2017/603.

Informed Consent: Retrospective study

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: U.D.H., F.G.Ö., Design: M.S.S., U.D.H. Literature Search: A.S., K.E., Data Collection and Process: U.D.H., K.E., Analysis or Interpretation Writing: U.D.H. Analyze: A.S., U.D.H., F.G.Ö., Literature Search: A.S., K.E., Writing: U.D.H., F.G.Ö.

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