ORIGINAL ARTICLE

CONTENTS

Interleukin-17 as predictor mortality of septic patients: a systematic review and meta-analysis

Dwi Retnoningrum[1], Budi Mulyono[2], Umi Solekhah Intansari[2], Ardhea Jaludamascena[3]

[1] UNIVERSITAS DIPONEGORO, SEMARANG, INDONESIA

[2] GADJAH MADA UNIVERSITY, BULAKSUMUR, INDONESIA

[3] DR. KARIADI HOSPITAL, SEMARANG, INDONESIA

ABSTRACT

Aim: This study aimed to prove the role of IL-17 on the clinical outcomes of septic patients.

Materials and Methods: This study used a systematic review and meta-analysis design. Data were obtained by searching articles published between January 2001 and June 2022 in Pubmed, Science Direct, Scopus, and Medline databases to evaluate Interleukin-17 on clinical outcomes in septic patients. Only human studies were used in this study. Meta-analysis was undertaken using random effects models.

Results: Fourteen published studies were eligible, and four studies were included in the meta-analysis. Meta-analysis of the ratio of means (RoM) IL-17 concentration demonstrated a 5.96-fold higher level in non-survivor septic patients compared with survivors (four studies; n = 194 patients; RoM=5.96; 95% CI, 3.51-10.31; $p < 0.00001$; $I^2 = 92\%$).

Conclusions: IL-17 levels were significantly elevated in non-survivor and predicted mortality of septic patients.

KEY WORDS: Cytokine, Interleukin-17, sepsis

Wiad Lek. 2024;77(6):1134-1140. doi: 10.36740/WLek202406104 DOI

INTRODUCTION

Sepsis is a syndrome that occurs in patients with systemic infection and often happens in critically ill patients. Thus, it requires appropriate markers and initial therapy to reduce its mortality rate. The mortality of sepsis varies between 25-30% of sepsis and 40-50% of septic shock [1,2]. The incidence of sepsis in the United States is around 300 cases per 100.000 population, of which 50% are undergoing treatment in Intensive Care Units[3]. The epidemiological trend of sepsis in Spain shows that the incidence of sepsis has increased from 3.3 per 1000 population in 2000 to 4.45 in 2013, with an increase in mortality from 6.34 to 7.89 per 1,000 population [4]. A 2009 study conducted by Phua et al, from 150 intensive care units in 16 countries in Asia, showed that severe sepsis was diagnosed in 10.9% of intensive care patients, with a mortality rate of 44.5% [5].

The pathogenesis of sepsis begins with the presence of infectious agents that enter blood circulation causing a systemic inflammatory state, but the presence of pathogens in the systemic circulation is not always present in cases of sepsis, the presence of inflammatory mediators released systemically can induce sepsis. While sepsis can be caused by various infectious agents, including bacteria, fungi, parasites, and viruses [6]. A study conducted by Vincent et al, in patients with infections in intensive care units (ICU), found that 70% of infection cases with positive culture results were 62% caused by Gram-negative bacteria, 47% by Gram-positive bacteria, and 19% by fungal infections [7].

Interleukin-17 is a pro-inflammatory cytokine produced by T helper-17, Natural Killer (NK) cells, CD-8 T cells, and neutrophils. IL-17 increases chemokine production which plays a major role in the recruitment of monocytes and neutrophils to the site of inflammation. This shows the important role of IL-17 as a proinflammatory cytokine in infectious conditions. Early studies of sepsis induction in animals demonstrated a distinct role for IL-17 [8,9]. Several systematic reviews and meta-analyses of IL-17 have been conducted on autoimmune diseases [10, 11]. Thus far, the researchers have not been able to find systematic review studies of IL-17 on sepsis that has been published, so the researchers want to conduct a systematic review and meta-analysis of the role of IL-17 in clinical outcomes in sepsis.

Table 1. Characteristic data of the study

Study (years)	Countries	Total subjects	Age (years)	Gender (male)%
Akin et al. 2015 (18)	Turkey	94	63 (19-87)	57 (60.6)
Ali et al. 2017 (19)	Egypt	100	32 (22-48)	80 (80)
Angurana et al. 2020 (20)	India	50	3.4 (0.95-7)	30 (60)
Bozza et al. 2007 (21)	Brazil	60	64 (51-75)	36 (60)
Chen et al. 2021 (22)	China	157	56.2±12.3	94 (59.9)
Dai et al. 2015 (23)	China	18	49.5 (28-67)	8 (44.4)
Guo et al. 2017(24)	China	48	50.6 ±11.9	30 (62.5)
Huang et al. 2016 (25)	Taiwan	76	71.3 ± 2.3	49 (64.5)
Lee et al. 2016 (26)	Korea	212	67.5 (29-95)	149 (70.3)
Liu et al. 2020 (27)	China	210	56.1 ± 12.3	145 (69.0)
Mikacenic et al. 2016 (28)	USA	140	54 ± 16	104 (74)
Na et al. 2019 (29)	China	219	56.5 ± 10.3	143 (65.3)
Rendon-Ramirez et al. 2015 (30)	Mexico	29	37.68 (± 11.56)	12 (41.4)
Wang et al. 2022 (31)	China	78	56.6 ± 11.4	49 (62.8)
White et al. 2010 (32)	Ireland	59	54 (72–80)	32 (54.2)
Wu et al. a 2015 (33)	Taiwan	52	72.31 ± 1.72	28 (54)
Wu et al. b 2011(34)	Taiwan	35	73.0 ± 3.2	24 (68.6)

AIM

This study aimed to prove the role of IL-17 on the clinical outcomes of septic patients.

MATERIALS AND METHODS

This study was a systematic review and meta-analysis, which evaluated interleukin-17 on the clinical outcomes of sepsis patients. The researchers referred to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram to search articles [12, 13]. While duplication of the same articles was detected using the Mendeley desktop software application [14]. The protocol was registered into the PROSPERO International Prospective Register of Systematic Reviews (Prospero) database (Registration number: CRD42022323950).

SEARCH STRATEGY

Literature searches were conducted on several databases: PubMed, ScienceDirect, Medline, and Scopus. This systematic review and meta-analysis used articles published from January 2001 to June 2022. Patient, intervention, comparison, and outcome (PICO) framework was used to facilitate the search strategy, with P: Sepsis OR Septic patients, I: Interleukin-17 OR IL-17, C: No comparison, and O: Mortality. Selected keywords such as "Interleukin-17" OR "IL-17" AND "sepsis" OR "septic" were used.

ELIGIBILITY CRITERIA

The inclusion criteria were 1) Articles written in English and were available in full-texts, 2) a study design that reported a prospective cohort with outcome assessment (survivors and non-survivors), and 3) measure serum or plasma IL-17 levels. The exclusion criteria were articles with experimental animal studies.

DATA EXTRACTION

Data extraction was made by summarizing the articles including the names of the researchers (years of publication of the articles), countries, study designs,

Table 2. Interleukin-17 level and outcome measurement

Study (year)	Specimen	Method	Sampling collection (hours)	Total sample	Outcome measurement	N Survivor	N Non-survivor	IL-17 Survivor (pg/ml)	IL-17 Non-survivor (pg/mL)
Akin et al (2015)	serum	ELISA	<12	94	28 days	64	30	0 (0-611.6)	11.3 (0-328.9)
Ali et al (2017)	serum	ELISA	3	100	28 days	84	16	NR	NR
Angurana et al (2020)	serum	ELISA	12	50	NR	45	5	237 (122-318)	400 (333-563)
Bozza et al (2007)	plasma	Bio-plex system	<24	60	28 days	31	29	0.0 (0.0-0.0)	0.0 (0.0-0.2)
Chen et al (2021)	serum	ELISA	<24	157	28 days	125	32	NR	NR
Dai et al (2015)	serum	ELISA	<24	18	28 days	15	3	186.4 ±110.7	308.1 ± 175.3
Guo et al (2017)	plasma	ELISA	6	48	28 days	36	12	36.0 ± 13.7	54.0±15.3
Huang et al (2016)	plasma	ELISA	<24	76	28 days	54	22	8.1 ± 2.6	19.3 ± 8.9
Lee et al (2016)	serum	ELISA	<24	212	28 days	155	57	6.8 (1.8-317.1)	5.3 (1.9-91.2)
Liu et al (2020)	serum	ELISA	<24	210	28 days	172	38	NR	NR
Mikacenic et al (2016)	plasma	CLIA	<24	140	28 days	114	26	NR	NR
Na et al (2019)	plasma	ELISA	<24	219	28 days	163	56	NR	NR
Rendon-Ramirez et al (2015)	serum	Milliplex MAP	<24	29	28 days	13	16	NR	NR
Wang et al (2022)	serum	ELISA	<24	78	28 days	63	15	NR	NR
White et al (2010)	serum	ELISA	<24	59	NR	41	18	31 (20.4–31)	25.7 (18.2–38.5)
Wu et al a (2015)	plasma	ELISA	<48	52	28 days	38	14	3.12 ± 1.06	4.85 ± 3.01
Wu et al b (2011)	plasma	ELISA	<48	35	28 days	23	12	8.7 (0.0 -131.6)	14.4 (0.0 -197.0)

NR: not reported.

patient demographics, and IL-17 levels. The summary of the research articles was tabulated alphabetically. The article summary was analyzed for IL-17 measurements and patient clinical outcomes (survivors versus non-survivors) in the study objectives and results.

Nominal variable data were presented as a proportion by percentage, whereas continuous data were presented as mean ± SD (standard deviation), median interquartile range (IQR), or range (minimum-maximum). The results were described in quantitative and qualitative summaries. In this study, the heterogeneity test was found to be less than 0.05 or large I^2 so the analysis model used was the random effects model (REM). Continuous data were calculated as a ratio of means (RoM) for each study and a meta-analysis was carried out using the generic inverse variance method (DerSimonian and Laird) to produce pooled measures of association, with 95% confidence interval (95% CI) and forest plots[15].

STATISTICAL ANALYSIS

Statistics with a significance of 0.05 and a confidence interval, and statistical heterogeneity used the I^2 statistic. Data analysis used Microsoft Excel and Review Manager version 5.4 [16]. Risk of bias assessment was performed using Quality in Prognostic Studies (QUIPS) to assess cohort studies for the association of IL-17 levels with clinical outcome (survivor vs non-survivor)[17].

RESULTS

The flow of research selection is presented in Fig. 1. The articles that belong to the inclusion and exclusion criteria for qualitative synthesis were 17 articles, and 4 articles were followed by meta-analysis.

The characteristics of each study are presented in Table 1. The results of the qualitative analysis of the 17 studies showed that the number of subjects was 1637 sepsis patients. One study (Angurana et al) was a study with the subject of sepsis in children, while the others had adult sepsis patients as their subjects. The IL-17 examination carried out in the research method of each study mostly used the Enzyme-linked immunosorbent assay (ELISA) method in 14 studies. One study with the Chemiluminescence immunoassay (CLIA) method (28)

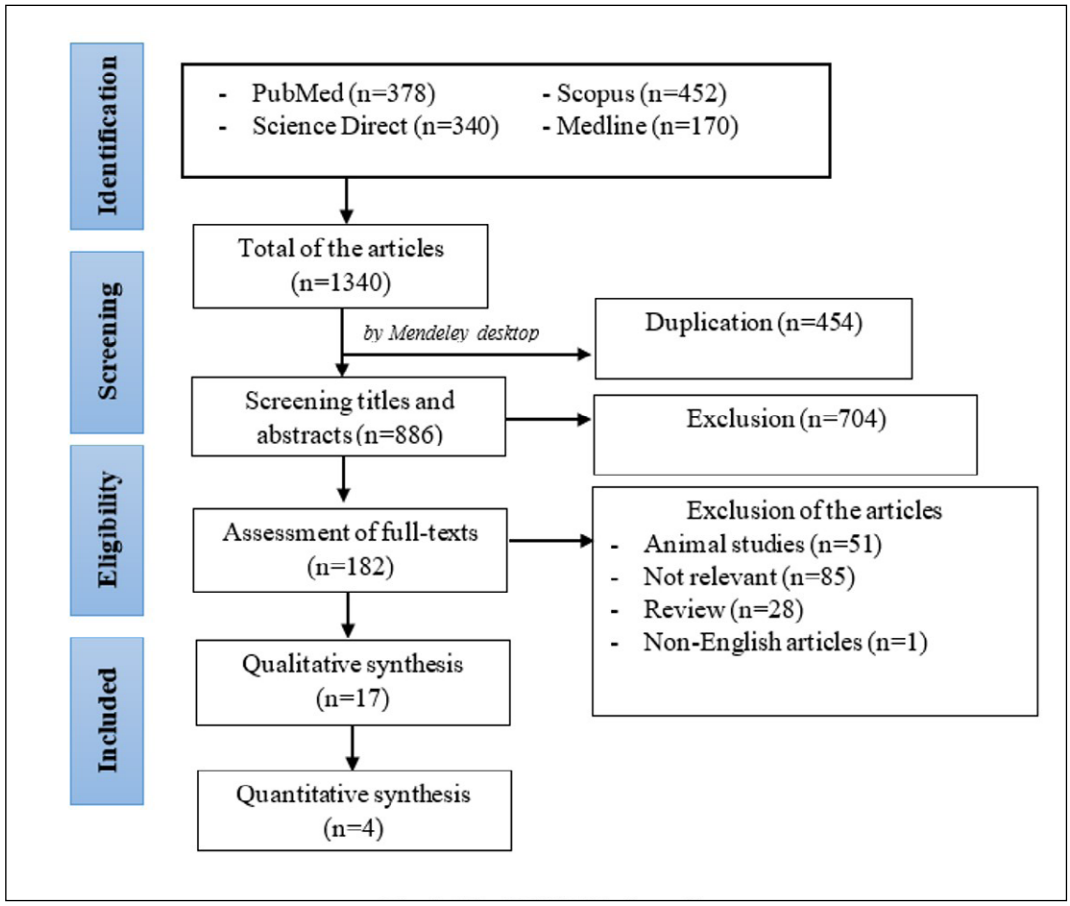

Fig.1. The PRISMA flow diagram.

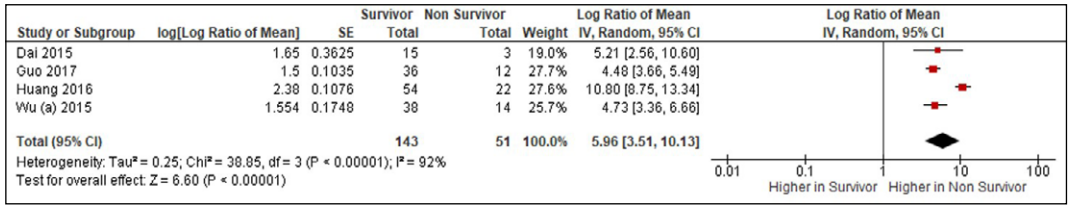

Fig. 2. Forest plot of IL-17 in survivor vs non-survivor.

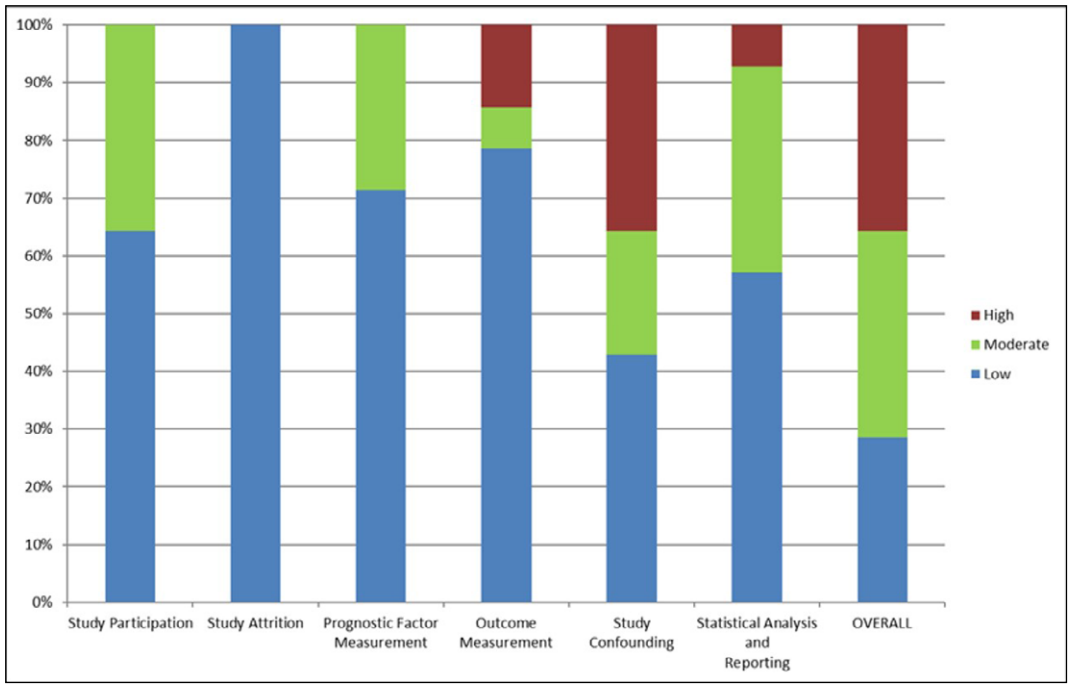

Fig. 3. Assessment risk of bias with QUIPS.

acute respiratory distress syndrome 1, two studies used the multiplex immunoassay system (21,30). Fifteen of the 17 sampling studies were undertaken for less than 24 hours during the treatment period, while 2 studies less than 48 hours. Survivor and non-survivor status for the majority of the study were followed within 28 days of treatment (88.2%). Seven studies did not obtain data on IL-17 levels between survivors and non-survivors, and 6 studies did not present the mean ± SD so 13 studies could not be continued to be quantitatively analyzed by meta-analysis (Table 2).

Based on the clinical outcome of patients with sepsis after 28 days of treatment, it was found that patients with 28 days of death (non-survivors) had higher IL-17 levels of 5.96 times compared to patients who were alive (survivors) (4 studies; n=194 patients; RoM = 5.96; 95% CI, 3.51-10.13; p <0.00001; I2 = 92%). The results were presented on the Forest plot (Fig. 2) as the result of a combined line when each study was plotted in one axis, the results of the log Ratio of Means (RoM), standard error (SE), and weight of each study were described. After a meta-analysis of the heterogeneity test, it was found that the p-value was <0.00001 with I^2 92% which indicates that there was large heterogeneity between studies (subgroups).

Assessment of risk of bias was carried out using Quality in Prognostic Studies (QUIPS) to assess cohort studies for the association of IL-17 levels with clinical outcomes (survivors and non-survivors)[17]. Based on the assessment of the risk of bias in each study, it was found that 6 studies had a high risk of bias, 6 studies had moderate bias and 5 studies had a low risk. The risk analysis for bias is shown in Fig. 3.

DISCUSSION

Most of the patients in each study were males. This was consistent with several other studies which showed a higher percentage of sepsis in males, 55% in the Shankar-Hari et al, 63% in the Lie et al, and 60.1% in the Sakr et al[18-20]. Most studies with adult sepsis patients occur at an older age because more comorbidities increased morbidity and mortality in sepsis. Alvaro-Meca et al, reported in an epidemiological study of sepsis in Spain that the incidence and mortality of sepsis increased in old age (50-59 years), increased at the age of 65 years, and was highest in the elderly over 85 years. The case fatality rate (CFR) in children was 7.2%, increasing to 20% at the age of 45-49 years and 30% at the age of 65 years[4].

The IL-17 levels from the meta-analysis found that non-survivor patients were 5.96 times higher than in survivors. The mechanism of high IL-17 in septic patients remained unknown. Interleukin-17 plays an important role in defense against bacteria produced by T cells, neutrophils, and some other cells by increasing the production of chemokines which play a role in the recruitment of neutrophils and monocytes to the tissue of the infection site. In addition, IL-17 plays a role in the production of other proinflammatory cytokines. Several animal studies have shown susceptibility to sepsis in states of IL-17 deficiency. However, this systematic review shows that elevated levels of IL-17 were associated with mortality in septic patients. The important role of IL-17 in the inflammatory response is the mobilization of neutrophils to the site of infection and the induction of the release of other proinflammatory cytokines. This is an important defense against infection with microorganisms [21].

Neutrophils are considered part of the first line of the immune system. Neutrophils can be found in the bloodstream, with a lifespan of 6-8 hours, and in tissues, that can last up to 7 days. The mechanisms that neutrophils use for host defense are phagocytosis, degranulation, cytokine production, and, most recently described, the production of neutrophil extracellular trap (NET). NETs are DNA structures that are released due to the decondensation and dispersal of chromatin, and thus occupy three to five times the volume of condensed chromatin. Several proteins attach to the NET, including histones and more than 30 primary and secondary granular components, including components with bactericidal activity such as elastase, myeloperoxidase, cathepsin G, lactoferrin, pentraxin 3, gelatinase, proteinase 3, LL37, peptidoglycan-binding protein, and others with bactericidal activity capable of destroying virulence factors [21]. Mobilization of neutrophils to the site of infection causes NETosis which can affect the clinical outcome of sepsis.

Increased levels of IL-17 as a proinflammatory cytokine excess caused hyperinflammatory conditions and a poor prognosis in the survival of patients with sepsis. Akin et al study reported an association of IL-17 with other markers of inflammation, IL-17 was associated with TNFα (p <0.001, r = 0.39), C-reactive protein (p = 0.014), and procalcitonin levels (p = 0.011)[18]. High levels of IL-17 in sepsis and there are research results showing that non-survivors had high levels of IL-17 in less than 48 hours of the initial examination of patients with sepsis provided an overview as a prognostic factor in patients with sepsis to the stage of severe sepsis or the occurrence of MODS. Examination of IL-17 levels in septic patients was expected to assist in determining therapeutic management to reduce patient morbidity to severe conditions or mortality in septic patients.

There were several limitations to this systematic review and meta-analysis study. The research was

obtained only from the database of international publications in English, while the unpublished studies or gray literature were not searched for data sources. The method of IL-17 examination was not entirely the same so it could cause examination bias. The etiology and severity of sepsis were not the same and might affect clinical outcomes.

CONCLUSIONS

Interleukin-17 was significantly higher in non-survivor sepsis patients than in survivor patients. Further research is needed to include the gray literature and in various languages. Measurement of IL-17 with a standardized method and the severity of sepsis should be considered in future studies.

REFERENCES

1. Vincent JL, Opal SM, Marshall JC, Tracey KJ. Sepsis definitions: Time for change. Lancet. 2013;381(9868):774–5. doi: 10.1016/S0140-6736(12)61815-7. DOI
2. Cohen J, Vincent JL, Adhikari NKJ et al. Sepsis: A roadmap for future research. Lancet Infect Dis. 2015;15(5):581–614. doi:10.1016/S1473-3099(15)70112-X. DOI
3. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. Virulence. 2014;5(1):1–11. doi: 10.4161/viru.27372. DOI
4. Álvaro-Meca A, Jiménez-Sousa MA, Micheloud D S et al. Epidemiological trends of sepsis in the twenty-first century (2000-2013): An analysis of incidence, mortality, and associated costs in Spain. Popul Health Metr. 2018;16(1):1–11. doi: 10.1186/s12963-018-0160-x. DOI
5. Phua J, Koh Y, Du B et al. Management of severe sepsis in patients admitted to Asian intensive care units : prospective cohort study. BMJ. 2011;342:d3245. doi: 10.1136/bmj.d3245. DOI
6. Burkovskiy I, Sardinha J, Zhou J, Lehmann C. Cytokine release in sepsis. Adv Biosci Biotechnol. 2013;4:860–865. doi: 10.4236/abb.2013.49114. DOI
7. Vincent J, Marshall J, Anzueto A et al. International Study of the Prevalence and Outcomes of Infection in Intensive Care Units. JAMA. 2009;302(21):2323–9. doi: 10.1001/jama.2009.1754. DOI
8. Flierl MA, Rittirsch D, Gao H et al. Adverse functions of IL-17A in experimental sepsis. FASEB J. 2008;22(7):2199–205. doi: 10.1096/fj.07-105221. DOI
9. Ogiku M, Kono H, Hara M et al. Interleukin-17A Plays a Pivotal Role in Polymicrobial Sepsis According to Studies Using IL-17A Knockout Mice. J Surg Res. 2012;174(1):142–9.
10. Hofmann MA, Kiecker F, Zuberbier T. A systematic review of the role of interleukin-17 and the interleukin-20 family in inflammatory allergic skin diseases. Curr Opin Allergy Clin Immunol. 2016;16(5):451–7. doi: 10.1097/ACI.0000000000000310. DOI
11. Acharya P, Mathur M. Interleukin-17 level in patients with vitiligo : A systematic review and meta-analysis. Australas J Dermatol. 2020;61(2):e208-e212. doi: 10.1111/ajd.13233. DOI
12. Tawfik GM, Agus K, Dila S et al. A step by step guide for conducting a systematic review and meta-analysis with simulation data. Trop Med Health. 2019;6:1–9. doi: 10.1186/s41182-019-0165-6. DOI
13. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Int J Surg. PLoS Med. 2009;6(7):e1000097. doi: 10.1371/journal.pmed.1000097. DOI
14. Mendeley Dekstop. Elsevier. 2018. www.mendeley.com [Accessed 02 December 2023]
15. Friedrich JO, Adhikari NKJ, Beyene J. Ratio of means for analyzing continuous outcomes in meta-analysis performed as well as mean difference methods. J Clin Epidemiol. 2011;64(5):556–64. doi:10.1016/j.jclinepi.2010.09.016. DOI
16. The Cochrane Collaboration. Review Manager (RevMan) [Computer program]. Version 5.4. 2020.
17. Hayden JA, Windt DA Van Der, Cartwright JL, Co P. Assessing Bias in Studies of Prognostic Factors. Ann Intern Med. 2013;158:280–6. doi: 10.7326/0003-4819-158-4-201302190-00009. DOI
18. Akin H, Akalin H, Budak F et al. Alterations of serum cytokine levels and their relation with inflammatory markers in candidemia. Med Mycol. 2015;53(3):258–68. doi: 10.1093/mmy/myu084. DOI
19. Ali MA, Abdelkader ESMA, El LMR. Interleukin-17 as a predictor of sepsis in polytrauma patients : a prospective cohort study. Eur J Trauma Emerg Surg. 2017. doi:10.1007/s00068-017-0841-3. DOI
20. Angurana SK, Bansal A, Muralidharan J et al. Cytokine Levels in Critically Ill Children With Severe Sepsis and Their Relation With the Severity of Illness and Mortality. J Intensive Care Med. 2021;36(5):576-583. doi: 10.1177/0885066620912989. DOI
18. Shankar-Hari M, Harrison DA, Rubenfeld GD, Rowan K. Epidemiology of sepsis and septic shock in critical care units : comparison between sepsis-2 and sepsis-3 populations using a national critical care database. BJA. 2017;119(4):626–36. doi:10.1093/bja/aex234. DOI
19. Lie KC, Lau C, Chau NVV et al. Utility of SOFA score , management and outcomes of sepsis in Southeast Asia : a multinational multicenter prospective observational study. J Intensive Care. 2018:6:9. doi: 10.1186/s40560-018-0279-7. DOI
20. Sakr Y, Jaschinski U, Wittebole X et al. Sepsis in intensive care unit patients: Worldwide data from the intensive care over nations audit. Open Forum Infect Dis. 2018;5(12):1–9.

21. Delgado-Rizo V, Martínez-Guzmán MA, Iñiguez-Gutierrez L et al. Neutrophil extracellular traps and its implications in inflammation: An overview. Front Immunol. 2017:8:81. doi: 10.3389/fimmu.2017.00081.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Dwi Retnoningrum
Universitas Diponegoro
Semarang City, Central Java, Indonesia
e-mail: dwiretno@fk.undip.ac.id

ORCID AND CONTRIBUTIONSHIP

Dwi Retnoningrum: 0000-0003-1606-0078 A B C D
Budi Mulyono: 0000-0002-0153-6427 E F
Umi Solekhah Intansari: 0000-0003-0646-4781 A E F
Ardhea Jaludamascena: 0009-0003-6744-0553 B C D

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 24.12.2023
ACCEPTED: 27.04.2024