



Sequential organ failure assessment (SOFA) score as a predictor of acute kidney injury in COVID-19 patients: a systematic review and meta-analysis

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Background: The sequential organ failure assessment (SOFA) score is a tool used to describe organ failure in critically ill patients. Studies have showed that coronavirus disease 2019 (COVID-19) patients who develop predictor of acute kidney injury (AKI) often have an increased SOFA.

Objective: This study aimed to evaluate the potential of SOFA score as a predictor AKI in COVID-19 patients.

Methods: A systematic search was conducted on PubMed, Google Scholar, EBSCO-Host, and ProQuest. The risk of bias was assessed using the Newcastle-Ottawa Scale.

Result: Out of the 9 studies reviewed, 7 showed a significant association between SOFA score and AKI. The meta-analysis of 3 studies gave mean differences of 1.66 in favor of the AKI group (95% CI 1.12 - 2.21). The heterogeneity was low (Tau² result = 0.06, I² result = 22% with p = 0.28) and the significant results for the overall effect showed a value of p < 0.00001.

Conclusion: The SOFA score has the potential to be a good predictor of AKI development in COVID-19 patients, with a significant mean difference.

Keywords: AKI, COVID-19, SOFA score, predictor.

INTRODUCTION

In December 2019, the first outbreak of the coronavirus disease 2019 (COVID-19) was reported in Wuhan, China.^{1,2} The rapid spread of the disease has become a global pandemic,³ with a total of 90,054,813 confirmed cases and over 1,945,610 deaths as reported by the World Health Organization (WHO) as of 13th January 2021.⁴ COVID-19 patients may exhibit a range of symptoms from mild respiratory distress to acute respiratory distress syndrome (ARDS), shock, and exacerbations of comorbidities. Previous investigations have shown that up to 33% of hospitalized COVID-19 patients develop ARDS. Tzotzos et al., found that acute kidney injury (AKI) is the most common extrapulmonary complication among ARDS patients.^{5,6} AKI in COVID-19 patients often exhibited severe stages and increased risk of mortality. A significant portion of survivors also experienced abnormal kidney function upon discharge. Therefore, predicting the incidence of AKI in critically ill COVID-19 patients is of great clinical interest to reduce

mortality and morbidity.

Multiple mechanisms have been postulated for the occurrence of AKI in COVID-19 patients, including viral cytopathic effect, hemodynamic compromise, the ARDS-AKI axis, glomerular injury, and rhabdomyolysis. The high expression of angiotensin converting enzyme-II (ACE2) protein in the human kidney was also believed to be critical for mediating cellular entry of SARS-CoV-2.⁷⁻⁹ Other mechanisms included the occurrence of a cytokine storm after a viral infection that can influence the kidney directly and indirectly through sepsis, shock, hypoxia, hemodynamic compromises, and rhabdomyolysis. This mechanism was supported by the prevalence of septic AKI in approximately 51–64% of patients with sepsis.¹⁰

Sequential organ failure assessment (SOFA) is a common assessment tool in the clinical management of critical patients. It was first introduced in 1996 to observe the degree of organ dysfunction. SOFA evaluates 6 major organ functions, namely circulation,

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respiration, liver, renal function, central nervous system, and coagulation profile. The score of each organ ranged from 0 (normal) and 4 (mostly abnormal).¹¹ Generally, the SOFA score is considered an effective method for describing organ failure in critically ill patients, and repeated scoring enables the estimation of disease progression and mortality risk.¹²

Recently, several studies have reported an increased SOFA score among COVID-19 patients who develop AKI. The SOFA score also has a good prognostic ability in predicting AKI, with a significant association when measured at baseline before the incident.¹³ Therefore, it can be used as a predictor of AKI incidence in COVID-19 patients. This systematic review and meta-analysis were conducted to evaluate the potential of SOFA score as a predictor of AKI in COVID-19 patients.

MATERIAL AND METHODS

This systematic review was designed and conducted in line with the guideline based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.

Eligibility criteria

Types of studies

The analysis included randomized-controlled trials, cross-sectional, cohort, and case-control studies. However, reviews, case reports, case series, conference abstracts, book sections, and commentaries/ editorials were excluded. Laboratories and non-human studies were not included. The articles with unavailable full-text, languages other than English, and irrelevant topics were also omitted.

Participants

All adult patient diagnosed with COVID-19 who developed AKI based on KDIGO Clinical Practice Guideline for Acute Kidney Injury were included without limitation for age, gender, race, comorbidities, and history of treatment. The control group is adult patients diagnosed with COVID-19 who didn't develop AKI throughout the disease.

Variables of interest

This study aimed to evaluate SOFA score as a predictor of AKI in COVID-19 patients. The inclusion criteria were studies on the score measurement conducted before the incidence of AKI and modified SOFA score that excluded renal components. Diagnosis of AKI should be carried out based on the KDIGO Clinical Practice Guideline for Acute Kidney Injury.

Outcome of interest

The outcome of interest in this study was the difference in SOFA score among AKI and non-AKI groups in form of

mean, median, p-value, and odds ratio. Furthermore, the odds ratio that had passed through control for other independent variables was extracted.

Search strategy and study selection

A literature search was carried out using several search engines, including Pubmed, Google Scholar, EBSCO-Host, and ProQuest, up to the year 2020. The studies were identified by five independent authors using the medical subject heading, namely Acute Kidney Injury, COVID-19, and Sequential Organ Failure Assessment Score. The following text and keywords are examples for all databases except Google Scholar:

((("acute kidney injuries" OR "acute renal injury" OR "acute renal injuries" OR "acute renal insufficiencies" OR "Acute renal insufficiency" OR "Acute kidney insufficiency" OR "Acute kidney failures" OR "Acute renal failure" OR "acute renal failures" OR "Acute kidney failure" OR "AKI")) AND ((("Sequential Organ Failure Assessment Scores" OR "Sequential Organ Failure Assessment Score" OR "SOFA Score" OR "SOFA Score" OR "SOFA" OR "modified SOFA" OR "modified SOFAS" or "non renal SOFA" or "non-renal SOFA")) AND ((("COVID 19" OR "Covid-19" OR "COVID 19 Virus" OR "coronavirus" OR "corona virus" OR "COVID-19 Virus" OR "COVID-19 infection" OR "COVID-19 infections" OR "2019-nCoV" OR "2019 nCoV" OR "Coronavirus Disease-19" OR "Coronavirus Disease 19" OR "2019 Novel Coronavirus" OR "2019-nCoV" OR "COVID19" OR "Coronavirus Disease 2019" OR "SARS Coronavirus 2" OR "SARS-CoV-2" OR "SARS COV 2" OR "COVID-19 Pandemic" OR "COVID 19 pandemic" OR "COVID-19 pandemics"))).

For Google Scholar, a similar literature search was performed using the variants of the keywords "Acute Kidney Injury", "COVID-19", "Sequential Organ Failure Assessment Score". All of the search outputs were exported into the Mendeley reference manager software. After duplicate removal, retrieved articles were screened based on their titles and abstracts. Subsequently, potentially eligible articles were thoroughly assessed in full text using the eligibility criteria as described above and any emerging discrepancies were resolved among the review team.

Data collection and extraction process

The studies included studies were analyzed and the data extracted were first author, country of origin, study design, age, gender, AKI criteria, types of SOFA score, sample sizes, and odds ratio.

Risk of Bias Assessment

Each study assessed using the NewCastle-Ottawa scale for cohort studies. The tool consisted of three main domains,



namely selection, comparability, and outcome, and the criteria of each domain can be found in the supplementary material. Each article was assessed by two reviewers independently and any discrepancies were discussed among the whole review team until a consensus was reached.

Conversion of the final score was based on the following classification, namely good quality when 3 or 4 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain, fair quality, 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain, poor quality, 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

Summary measures

SOFA score for each COVID-19 patient was measured and reported in numerical (continuous) data for both AKI and non-AKI groups. The score was expressed in mean \pm standard deviation for normally distributed data or median (interquartile range) for non-normally distributed data. Odds ratio (OR) or hazard ratio (HR) and 95% confidence interval (95% CI) were extracted to represent the effect size. Furthermore, the p-value was included for each item to show the significance of the results.

Synthesis of results

Both univariate and bivariate results were presented. In the univariate table, the patient's age and sex were included as demographic characteristics, along with the total population, country, and the type of each study, as well as the classification of AKI and the type of SOFA score. These results were further elaborated and discussed, with the confounding factors interfering with the occurrence of AKI. Bivariate results were tabulated and sorted according to the occurrence of AKI during a hospital stay and their respective SOFA score from each study.

Statistical Analysis

A meta-analysis was conducted on studies that reported the mean difference of SOFA score between AKI and Non-AKI patients. Bivariate data were analyzed using a random effect model by Software Review Manager 5.4 and presented as a forest plot with Mean Difference (MD) as the effect size estimate. The random effects meta-analyses were used, which were considered more powerful than fixed effects analyses. This was because extrapolation can be made for the results to a larger sample of the population in cases when new study is conducted in this area. A funnel plots test was carried out to inspect the potential publication bias, while sensitivity analysis was performed to reduce uncertainty and search for errors in the model.

RESULT

The variants of the keywords "AKI", "COVID-19", and "SOFA score", were used to search in PubMed, Google Scholar, EBSCO-Host, and ProQuest, up to the year 2020. A total of 686 records were identified, from which 591 remained

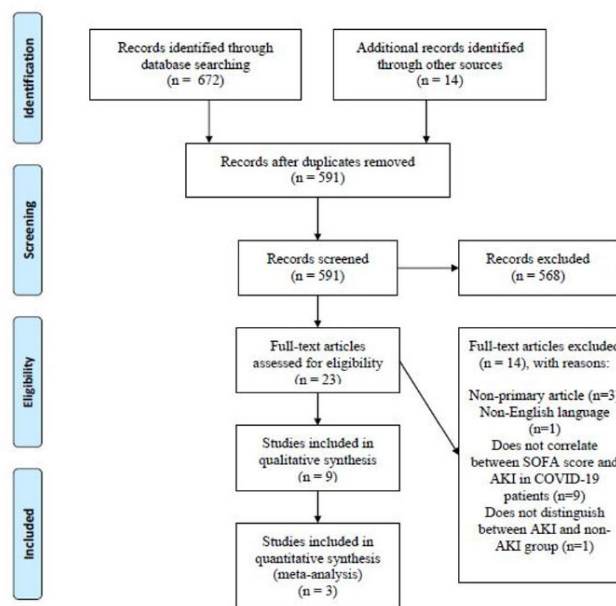


Figure 1. PRISMA 2009 diagram of studies selection.

Study	Selection				Comparability	Exposure			Conclusion
	S1	S2	S3	S4		E1	E2	E3	
Joseph et al. 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	Good
Cui et al. 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	Good
Rubin et al. 2020	☆	☆	☆	-	☆	☆	☆	☆	Good
Xu et al. 2020	☆	☆	☆	☆	☆☆	☆	☆	-	Good
Xia et al. 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	Good
Wang et al. 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	Good
Gaetano et al. 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	Good
Barragan et al. 2020	☆	☆	☆	☆	-	☆	☆	☆	Poor
Zhang et al. 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	Good

Notes: S1, Representativeness of the exposed cohort; S2, Selection of the non exposed cohort; S3, Ascertainment of exposure; S4, Demonstration that outcome of interest was not present at start of study; E1, Assessment of outcome; E2, Was follow-up long enough for outcomes to occur; E3, Adequacy of follow up of cohorts

Figure 2. Quality assessment.



Table 1. Study characteristics of the included studies

No.	Author, Year	Country	Types of Study	Population				Acute Kidney Injury Diagnosis Criteria	Sequential Organ Failure Assessment (SOFA) Score used as prognostic tools		
				N	Age	Sex	AKI				
				AKI	No-AKI	AKI	No-AKI				
1	Joseph et al, 2020 ¹⁴	France	Cohort retrospective	19	81	60 (54-68)	54 (45-61)	Male: 11 (58%) Female: 8 (42%)	Male: 59 (73%) Female: 22 (27%)	KDIGO clinical practices guidelines	SOFA score and non-renal SOFA score on admission
2	Cui et al, 2020 ¹⁵	China	Cohort retrospective	21	95	61.05 ±12.9	58.58 ±14.6	Male: 12 (57%) Female: 9 (43%)	Male: 54 (57%) Female: 41 (43%)	KDIGO clinical practices guidelines	SOFA score on admission
3	Rubin et al, 2020 ¹⁶	France	Cohort retrospective	57	14	61.7 ± 11.4	59.1 ± 15.0	Male: 46 (81%) Female: 11 (19%)	Male: 9 (64%) Female: 5 (36%)	KDIGO clinical practices guidelines	SOFA score on admission
4	Xu et al, 2020 ¹⁷	China	Cohort retrospective	263	408	66 (60-75)	64 (54-72)	Male: 173 (66%) Female: 90 (34%)	Male: 261 (64%) Female: 147 (36%)	KDIGO clinical practices guidelines	SOFA score on admission
5	Xia et al, 2020 ¹⁸	China	Cohort retrospective	41	40	69.6 ± 9.3	63.6 ± 12.7	Male: 30 (73.2%) Female: 11 (26.8%)	Male: 24 (60%) Female: 16 (40%)	KDIGO clinical practices guidelines	SOFA score sofa on admission
6	Wang et al, 2020 ¹⁹	China	Cohort retrospective	136	139	70 (64-78)	68 (58-74)	Male: 81 (59.6%) Female: 55 (40.4%)	Male: 80 (57.6%) Female: 59 (42.4%)	KDIGO clinical practices guidelines	SOFA score sofa on admission
7	Gaetano et al, 2020 ²⁰	Italy	Cohort retrospective	69	238	74.7 ± 9.10	62.4 ± 13.9	Male: 55 (79.7%) Female: 14 (20.3%)	Male: 164 (68.9%) Female: 74 (31.1%)	KDIGO clinical practices guidelines	SOFA score sofa and non-renal SOFA score on admission
8	Barragan et al, 2020 ²¹	France	Cohort retrospective	24	18	61.50 (55.5-65)	60.50 (49.75 - 66)	Male: 19 (79.2%) Female: 5 (20.8%)	Male: 15 (83.3%) Female: 3 (16.7%)	KDIGO clinical practices guidelines	SOFA score on admission
9	Zhang et al, 2020 ²²	China	Cohort retrospective	123	159	71 (62-79)	68 (57-74)	Male: 70 (56.9%) Female: 53 (43.1%)	Male: 85 (53.5%) Female: 74 (46.5%)	KDIGO clinical practices guidelines	SOFA score on admission

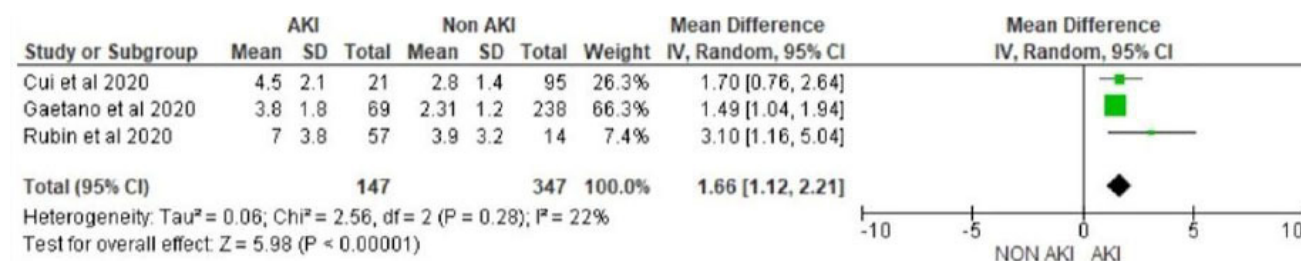
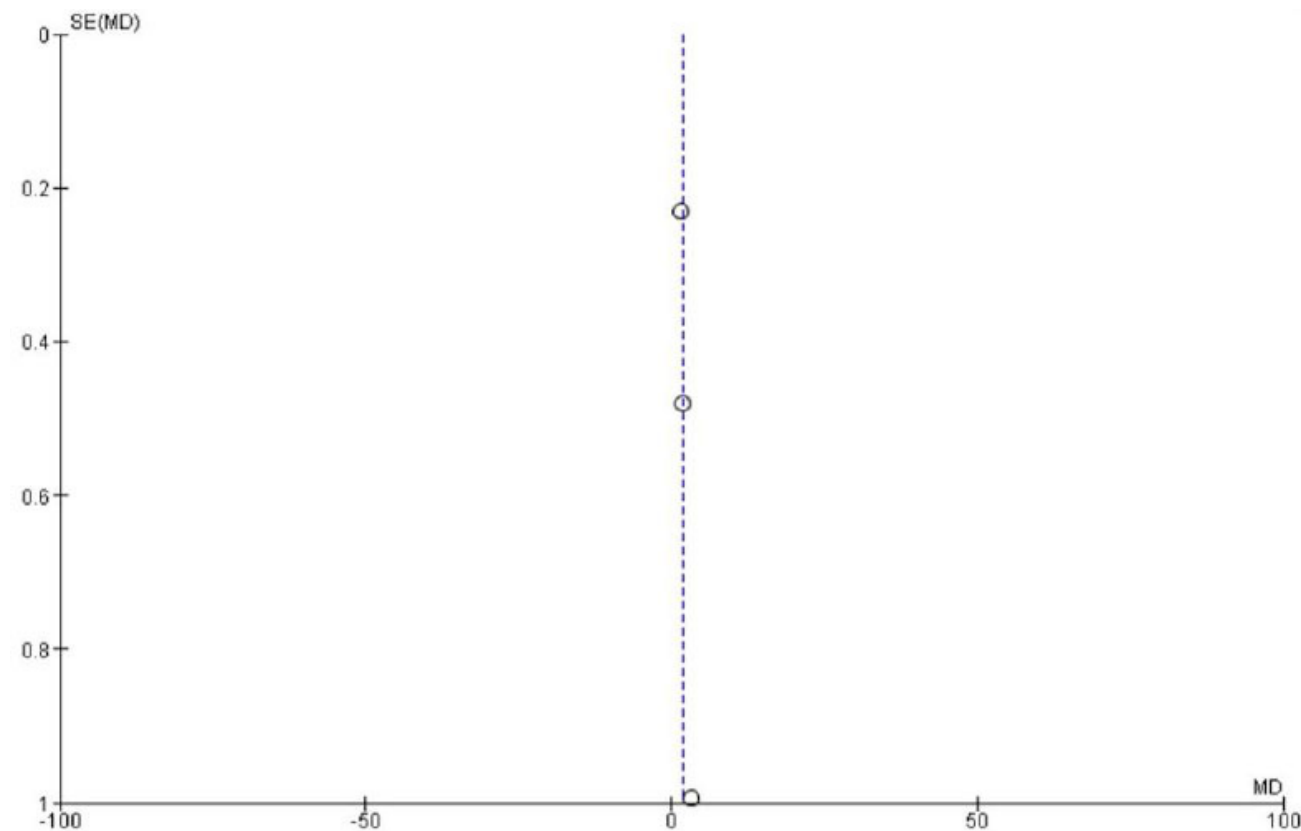
**Table 2.** The result of SOFA score between AKI and non-AKI groups in COVID-19 patients

No	Author, Year	SOFA Score Results				
		AKI*	No-AKI*	p-value**	OR***	95% CI (Upper-Lower)
1	Joseph et al., 2020 ¹⁴	5 (2-7)	2 (2-3)	0.003	1.29	1.040-1.700
2	Cui et al., 2020 ¹⁵	4.5±2.1	2.8±1.4	0.002	1.498	1.047-2.143
3	Rubin et al., 2020 ¹⁶	7 ± 3.8	3.9 ±3.2	0.006	N/A	N/A
4	Xu et al., 2020 ¹⁷	4 (3-6)	3 (1-4)	< 0.001	N/A	N/A
5	Xia et al., 2020 ¹⁸	7 (5-10)	6 (4-8)	0.03	N/A	N/A
6	Wang et al., 2020 ¹⁹	5 (4-8)	5 (2-6)	0.278	1.058	0.995-1.172
7	Gaetano et al., 2020 ²⁰	3.8±1.8	2.31±1.2	< 0.0001	2.52***	1.21-5.23
8	Barragan et al., 2020 ²¹	4.5 (3-8.5)	8 (4-9.75)	0.134	N/A	N/A
9	Zhang et al., 2020 ²²	4 (3-7)	1 (1-3)	<0.001	1.643	1.436-1.881

*Data presented as mean ± SD or median (IQR)

**p-value for the difference of mean or median. p-value <0.05 is considered significant.

***Data presented as Hazard Ratio if no OR was provided

**Figure 3.** Forest plot with mean differences (95% CI) of SOFA score as a predictor of AKI in COVID-19 patients.**Figure 4.** Funnel plot with Standard Error (SE) of SOFA Score as a predictor of AKI in COVID-19 Patients.

after duplicate removal. Titles and abstracts were screened, leaving 23 potential studies. Full-text assessment of each 23 studies was evaluated for eligibility criteria and 14 was excluded because they did not distinguish between AKI and non-AKI group, evaluate SOFA score and AKI in COVID-19 patients, written in non-English, or is a non-primary article. The remaining 9 studies were included in the systematic review, while only 3 studies were used for the meta-analysis (Figure 1).

Quality Assessment

The results showed that 8 out of 9 studies were of good quality, while only the study by Barragan et al., was rated as poor quality due to a lack of adjustments for confounding variables (Figure 2).

Study Characteristics

There were 9 studies included in this systematic review and 3 were eligible for meta-analysis. Table 1 showed the details of the selected studies for the systematic review. All studies were retrospective cohort, half of which was conducted in China, 3 were conducted in France, and 1 was conducted in Italy. Furthermore, all studies diagnosed acute kidney injury based on KDIGO clinical practices guidelines. Among the included studies that reported SOFA scores, only 2 reported non-renal SOFA scores.

Final Results

Table 2 present the mean or median of SOFA score in AKI and non-AKI patients and the odd ratio. All studies except Barragan et al. and Wang et al. reported a significant difference in mean or median between the two groups.

Meta-Analysis

Only 3 studies reported outcome measures that were eligible for meta-analysis. Figure 3 presented the forest plot as meta-analysis outcomes, which evaluated the association between SOFA score as a predictor and AKI as the main outcome. Subsequently, the effect size was measured by Mean Difference (MD) using comparison data from the study group diagnosed with AKI compared to non-AKI as the control group. Each study was weighted using the Inverse Variance method to obtain a pooled MD with 95% CIs. A funnel plots test was carried out to inspect the potential publication bias, as illustrated in Figure 4. Meanwhile, sensitivity analysis was carried out to reduce uncertainty and search for errors in the model. Data were sorted by the name of the author, as shown in Figure 2.

Figure 4 illustrates the association between SOFA score as a predictor tool and AKI as the outcome of organ failure in COVID-19 patients. The MDs value of 1.66 from

the 3 included studies indicated that SOFA score differences favor the AKI group, with a 95% CI ranging from 1.12 to 2.21. The heterogeneity across studies based on the Q statistic was low (Tau² result = 0.06 and I² result = 22% with p = 0.28) and the significant results for the overall effect showed a value of p < 0.00001.

DISCUSSION

A total of three studies reported mean and standard deviation of SOFA score in AKI and non-AKI COVID-19 patients, while the remaining six presented the median and interquartile range. A meta-analysis was conducted on the three studies that presented the outcome as mean and standard deviation. The results showed a significant difference in SOFA score between AKI and non-AKI subjects with a mean difference of 1.66 favoring AKI.

Out of the nine studies eligible for the systematic review, seven studies showed significant p-values of mean or median differences of SOFA score between the AKI and non-AKI groups.^{14-18,20,22} Meanwhile, the remaining two studies demonstrated the opposite result.^{19,21} due to the small population size and the retrospective characteristic of the study that may cause inconsistencies in the diagnosis of AKI. There is still no consensus recommended for selecting reference creatinine. Therefore, there was heterogeneity in the selection of baseline serum creatinine among studies, which can underestimate the incidence of AKI in the subjects.^{19,21}

A total of four studies reported an odds ratio (1,058-1,498) and one stated hazard ratio.^{14,15,19,20,22} Among all the studies, the most commonly discussed confounding factors were chronic kidney disease (CKD), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), diabetes, and hypertension. Other factors included body mass index (BMI), immunocompromised status, heart failure, baseline creatinine, non-steroidal anti inflammatory drugs (NSAID), invasive mechanical ventilation, positive end expiratory pressure (PEEP) on day one, renal replacement therapy (RRT), vasopressor, IL-6 at day 0 (ng/mL), C3 at day 0 (ng/mL), C4 at day 0 (ng/mL), sC5b9 at day 0 (ng/mL), ferritin at day 0 (mg/L), fibrinogen at day 0 (g/L), chloroquine or hydroxychloroquine, eculizumab, lopinavir/ ritonavir, tocilizumab, NLR, and albumin. These factors were included in the statistical analysis when analyzing SOFA score as a predictor of AKI. Gilbert et al., also reported hypertension, CKD, and HIV infection as the most common risk factor. Meanwhile, Ceba et al., assessed risk factors, including age, diabetes, hypertension, baseline creatinine (mg/dL), heart failure, sepsis/SIRS, nephrotoxic drugs, the severity of disease, hypotension/shock, pressors/inotropes, high-risk surgery/emergency surgery, cardiopulmonary bypass time (minutes), IABP). The results showed a significant association



with the development of AKI in critically ill patients except for hypertension.^{23,24} Chronic kidney disease was also found to be one of the most important risk factors in the development of AKI.^{25,26} However, based on this review, only two studies showed a significant association between chronic kidney disease and the occurrence of AKI.^{20,21}

SOFA score can be used to measure organ dysfunction and as a predictor for AKI because it assesses renal components (creatinine and urine output) which are also used in KDIGO criteria to define AKI.²⁷ Similarly, Lee et al. (2018) found that the SOFA score has an excellent AUROC of 0.957 ($p < 0.001$), with 92.3% sensitivity and 88.9% specificity using a cut-off of 7.5 in predicting septic AKI in general patients.¹³ Zhang et al., also discovered that COVID-19 patients who developed AKI tended to have a higher score on day one. Meanwhile, after adjustment, the score was independently associated with the occurrence of AKI.²² A total of two studies also used the non-renal SOFA to avoid collinearity between predictor and outcomes.^{14,20} These studies found that non-renal SOFA were statistically significant predictors of AKI and a cut-off of >3 points was the strongest predictor.

The limitations of this systematic review and meta-analysis include the restriction of data presented in the meta-analysis to only three studies due to the lack of reports on mean \pm SD. There was difficulty in the accurate conversion of the median and interquartile range values to obtain the mean and SD because available data were insufficient to determine the distribution of the outcomes. Secondly, some studies did not report the onset of AKI, therefore, the SOFA score becomes less reliable for predicting AKI. Thirdly, several investigations failed to preclude the comorbidities due to their retrospective nature. However, this study was the first to investigate the potential role of SOFA score as a predictor of AKI. Published data in grey literature were also included, which were considered the strength of this systematic review.

This study suggests that there is a significant difference in the SOFA score between AKI and non-AKI COVID-19 patients. As AKI is the most common extrapulmonary manifestation in ARDS patients, including critically ill COVID-19 patients, further investigation is recommended regarding the use of SOFA score in predicting the occurrence of AKI. A larger cohort with a broader research field is needed to obtain more extrapolated results on the sensitivity and specificity of SOFA score in predicting AKI, and the optimal time to obtain SOFA score in COVID-19 patients. Moreover, clinicians are also recommended to routinely measure SOFA scores in COVID-19 patients as a simple tool for risk stratification and consider the result of this study.

CONCLUSION

This study found that most studies reported a significant association between SOFA score and AKI. The meta-analysis also demonstrated a significant mean difference in the SOFA score among AKI and non-AKI COVID-19 patients. Although several factors may interfere with the progression of AKI, five studies that passed through multivariate analysis to adjust the comorbidities showed that the SOFA score is independently associated with the occurrence of AKI.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS CONSIDERATION

This article was a review article therefore no ethical consideration has been made.

AUTHOR CONTRIBUTION

All authors shared equal contributions in this systematic review and meta-analysis, from conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, visualization, writing (original draft), and writing (review and editing).

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