Cytokine Storm score (CSs) in COVID-19 Patients Smokers at Dr. Saiful Anwar Malang

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Abstract

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Background : After 3 years of the COVID-19 pandemic, its escalation is still causing a critical global health problem. Cytokine storm is a severe complication of COVID-19, and smoking is a risk factor for death. The prevalence of smoking in Indonesia is very high, but there is still little research on the effect of smoking on the occurrence of cytokine storms. The Cytokines Storm Score (CSs) is a quick and simple method for detecting cytokine storms early by utilizing D-dimer, lactate dehydrogenase (LDH), ferritin, and C-reactive protein (CRP) parameters. The objectives of this study was to evaluate CSs in COVID-19 patients smokers

Methods : Retrospective analysis of 120 confirmed COVID-19 patients in November 2020–2021, divided into 2 groups (60 smokers and non-smokers), male, without comorbidities. analysis using Chi-square and Mann-Whitney. Prior to the CSs examination, lymphopenia is required. CSs were positive if at least two of the D-dimer, LDH, or ferritin levels were elevated. The CRP level is measured if there is an increase in only one of these values. Elevated CRP, lymphopenia, and impaired D-Dimer, LDH, or ferritin will result in positive CSs.

Results : CSs were significantly higher in smokers than non-smokers (54.5% vs. 45.5%, p = 0.024). D-dimer and CRP levels were significantly higher in smokers than non-smokers (1620 ng/mL vs. 1002.5 ng/mL, p = 0.001; and 13.8 mg/dL vs. 7.75 mg/dL, p = 0.001). Lower LDH and higher ferritin levels were not significant in smokers compared to non-smokers (405.5 IU/L vs. 418 IU/L, p = 0.160; and 886.65 ng/mL vs. 790.5 ng/mL, p = 0.203).

Conclusion : Cytokines Storm scores (CSs) increased significantly in COVID-19 patients who smoked, D-dimer and CRP levels were significantly higher in smoking COVID-19 patients compared to non-smokers**.**

Keywords : cytokine storm; COVID-19; Cytokine Storm score (CSs); smoker

INTRODUCTION

After three years, the COVID-19 pandemic is still causing serious problems for global health. Since June 2020, more than 7.26 million cases have been reported in 215 countries, with over 423,000 deaths and a global mortality rate of 5.6 percent.[1] Cytokines storm syndrome is a severe COVID-19 complication with smoking as a potential risk factor that can lead to death.[2] In these circumstances, a pandemic is critical for identifying risk factors, such as smoking, which is a risk factor for a variety of infections caused by bacteria and viruses.[3] Although smoking is very common in Indonesia, there is moderate little research on the link between smoking and cytokine storm incidents. Smoking in COVID-19 patients, such as adding an ingredient and burning it, could Improve the regulation of the angiotensin-converting enzyme-2 (ACE-2) receptor used by SARS-CoV-2 to enter the cell host, so that the more viruses that enter, the more Cytokines are activated, potentially leading to more symptoms in COVID-19 patients.[3] According to a study conducted at the hospital Saiful Anwar Malang, smoking is associated with a higher risk of COVID-19 development and mortality in COVID-19 patients who are hospitalized.[4] Based on the foregoing, a faster, simpler, and more accurate method of detecting cytokines storm is required, namely the Cytokines Storm score (CSs) with D-dimer, LDH, ferritin, and CRP parameters.

The Cytokine Storm score (CSs) is a biomarker guide that can be used as a prediction tool to identify patients at various stages of hyperinflammation, which may be useful for early intervention, early therapy, and disease progression prevention.[5] CSs were considered positive if lymphopenia was found and at least two of the serum levels of D-dimer, ferritin, or LDH were elevated.[6] D-dimer is a degradation product of fibrin, a small protein fragment that is present in the blood after the blood clot is degraded by fibrinolysis. Although the mechanism of this complication is still unknown, D-dimer shows relevance to the impact of smoking on the endothelium and COVID-19.[7] *Lactate Dehydrogenase* (LDH) is an intracellular enzyme involved in anaerobic glycolysis that catalyzes the oxidation of pyruvate to lactate.[8] The results showed that there was a significant increase in serum antioxidant enzymes, namely LDH, in the smoker group compared to the non-smoker group.[9] Ferritin is an acute-phase protein, a major iron storage protein. Based on research through *Bronchoalveolar Lavage* (BAL), it was found that in vitro ferritin release increased for 20 hours in alveolar macrophages obtained from mild smokers (p<0.05) and severe smokers (p< 0.001).[10] C-Reactive Protein (CRP) is an acute-phase inflammatory protein produced by the liver that can rise in a variety of conditions, including inflammation, cardiovascular disease, and infection.[11] Research shows that there is a dose-response relationship between CRP levels and the intensity and/or duration of smoking.[12]

This study aims to evaluate the CSs between smokers and non-smokers in COVID-19 patients using a scoring system based on a minimum of 2 from D-dimer, LDH, ferritin, or CRP levels (which meet the requirements).

METHODS

The design of this study was analytic retrospective, samples were obtained from 120 patients who were divided into 2 groups (60 smokers and 60 non-smokers). The research was conducted at the Dr. Saiful Anwar Malang in November 2020–2021. The inclusion criteria were: patients treated in the Integrated Covid Installation Room (intensive and non-intensive) as confirmed cases (RT-PCR Sars Cov 2 or TCM); age >18 years; male sex; smoker, former or non-smoker; Lymphocytes/Absolute Lymphocyte Count (ALC) <1000 (x103/mmc), and no comorbidities.

Data were analyzed using the one-sample Kolmogorov-Smirnov test for normality, the Chi-Square test for the categorical scale, and the Mann-Whitney test for the numerical scale. Lymphopenia was selected as a prerequisite for CSs, then if at least two levels of serum D-dimer > 1000 ng/mL, LDH > 300 IU/L, and ferritin >500 ng/mL were found, then CSs was considered positive. But in patients with lymphopenia and interference from only one of the D-dimer, ferritin, or LDH levels, then the CRP level is measured. If CRP is >10 mg/dL along with lymphopenia and increased D-dimer, ferritin, or LDH, then CSs is considered positive.

RESULTS

Characteristics Sociodemography CSs (+) in Smokers Based on the Brinkman Index (BI)

Sociodemographic characteristics with CSs (+) in smokers based on the Brinkman Index(BI): There were 55 subjects who were divided into 3 groups, namely mild, moderate, and severe (BI), as can be seen in Table 1.

Based on age with a mild Brinkman Index (BI), there were 5 (27.8%) aged 18–39 years, 11 subjects (61.1%) aged 40–64 years, and 2 subjects (11.1%) aged ≥ 65 years. In moderate (BI) there was 1 subject (3.2%) aged 18-39 years, 21 subjects (67.7%) aged 40–64 years, and 9 subjects (29.0%) aged ≥ 65 years. In severe (BI) there were no subjects aged 18–39 years, and 3 subjects (50.0%) aged ≥40–64 years.

Based on education with mild (BI), there were no subjects with elementary school education, 4 subjects (22.2%) in junior high school, 3 subjects (16.7%) in high school, and 11 subjects (61.1%) in undergraduate. In

TABLE 1
Sociodemographic Characteristics of CSs (+) in Smokers based on the Brinkman Index (BI)

Variables	Brinkman Index (CSs (+))						p value
	Mild		**Moderate**		**Severe**		
	(n=18)	%	(n=31)	%	(n=6)	%	
Age (year)							
18–39 years	5	27.8%	1	3.2%	0	0.0%	0.035
40–64 years	11	61.1%	21	67.7%	3	50.0%	
≥ 65 years	2	11.1%	9	29.0%	3	50.0%	
Education							
Primary School	0	0.0%	4	12.9%	3	50.0%	0.021
Junior High School	4	22.2%	5	16.1%	2	33.3%	
Senior High School	3	16.7%	10	32.3%	0	0.0%	
Bachelor	11	61.1%	12	38.7%	1	16.7%	
Profession							
Not working, retired, student	4	22.2%	11	35.5%	1	16.7%	0.256
Laborers, farmers, drivers	3	16.7%	6	19.4%	4	66.7%	
Entrepreneur, trader	4	22.2%	8	25.8%	1	16.7%	
Private sector employee	4	22.2%	5	16.1%	0	0.0%	
Health workers	1	5.6%	1	3.2%	0	0.0%	
Civil servants, lecturers, teachers	2	11.1%	0	0.0%	0	0.0%	

TABLE 2
Comparison of CSs in COVID-19 Patients Smokers and Non-Smokers

Smoker status	CSs (+)		CSs (-)		p value
	(n=101)	%	(n=19)	%	
Smoker	55	54.5%	5	26.3%	0.024
Non smoker	46	45.5%	14	73.7%	

If the value of p <0.05 = significant, Data analysis was performed using the Chi square test (categorical scale), CSs: *Cytokines Storm score*

moderate (BI), there were 4 subjects (12.9%) from elementary school, 5 subjects (16.1%) from junior high school, 10 subjects (32.3%) from senior high school, and 12 subjects (38.7%) from undergraduate school. In severe (BI), there were 3 elementary school subjects, 2 junior high school subjects, no subjects with high school education, and 1 subject (16.7%) was an undergraduate.

Based on work with mild (BI), it was found that 4 subjects (22.2%) had similarities, namely (not working, retirees and students), (self-employed and traders), and private employees, as many as 3 subjects (16.7%) laborers, farmers and driver, 1 subject (5.6%) health workers,

2 subjects (11.1%) lecturers, teachers, and civil servants. In moderate (BI), 11 subjects (35.5%) do not work, retirees and students, 6 subjects (19.4%) laborers, farmers and drivers, 8 subjects (25.8%) entrepreneurs and traders, 5 subjects (16, 1%) private employees, 1 subject (3.2%) health workers, no subjects as lecturers, teachers, and civil servants. In severe (BI), 1 subject (16.7%) has similarities: (not working, retired and students) and (self-employed and traders), 4 subjects (66.7%) are laborers, farmers, and drivers, there are no subjects as (employees private sector), (health workers) and (lecturers, teachers, and civil servants).

TABLE 3
Comparison of CSs in Smokers Based on Brinkman Index (BI)

Brinkman Index	CSs (+)		CSs (-)		p value
	(n=55)	%	(n=5)	%	
Mild	18	32.7%	2	40.0%	0.733
Moderate	31	56.4%	2	40.0%	
Severe	6	10.9%	1	20.0%	

If the value of p <0.05 = significant, Data analysis was performed using the Chi square test (categorical scale), CSs : *Cytokines Storm score*

TABLE 4
Levels of D-dimer, LDH, ferritin, and CRP in COVID-19 Patients: Smokers and Non-Smokers

Variables	std. Deviation	Minimum	Maximum	Median	p value
D-dimer (mg/L)					
Smoker	9858.37	450	37200	1620	0.000
No smoker	868.79	139	3720	1002.5	
Total	7379.63	139	37200	1311.25	
LDH U/L					
Smoker	433.11	142	2250	405.5	0.160
No smoker	327.29	103	1448	418	
Total	385.16	103	2250	411.75	
Ferritin ng/mL					
Smoker	1165.01	246.3	6665	886.65	0.203
No smoker	635.07	127	2173	790.5	
Total	947.29	127	6665	838575	
CRP (mg/dL)					
Smoker	11.25	0.9	57.9	13.8	0.000
No smoker	5.92	0.3	24.1	7.75	
Total	9.54	0.3	57.9	10.775	

If the value of p < 0.05 is significant, data analysis was performed using the Mann–Whitney test (numerical scale). Because the distribution is not normal, the median value (minimum-maximum) is used

Comparison of CSs in Smoker and Non-Smoker COVID-19 Patients

In the comparison of CSs in smoking and non-smoking COVID-19 patients, there were 120 subjects, consisting of 60 smokers and 60 non-smokers. The data uses a categorical scale, so the Chi-Square test is carried out with the results as described in Table 2.

Based on the data from the Table 2, it shows a significance value of (p = 0.024), so it can be interpreted that there is a significant difference between subjects who experience CSs (+) and CSs (-) in the smoker and non-smoker groups. The incidence of CSs (+) was significantly higher in smokers compared to non-smokers: 5 subjects (54.5%) vs. 46 subjects (45.5%). While the incidence of CSs (-) was significantly lower in smokers compared to non-smokers: 5 subjects (26.3%) vs. 14 subjects (73.7%).

Comparison of CSs in Smokers COVID-19 Patients Based on the Brinkman Index (BI)

Comparison of CSs in smokers based on the Brinkman Index obtained as many as 60 subjects, using categorical scale data, so that the Chi-Square test was carried out with

the results as described in Table 3.

The results of the comparison of the Brinkman Index between subjects who experienced CSS (+) and CSs (-) showed a significance value of 0.733 (p >0.05), so it could be interpreted that the results of the comparison of the Brinkman Index between subjects who experienced CSS (+) and CSs (-) did not find a meaningful difference. The incidence of CSs (+) was not significantly higher in moderate (BI) 31 subjects (56.4%) compared to mild (BI) 18 subjects (32.7%) and severe (BI) 6 subjects (10.9%). Meanwhile, the incidence of CSs (-) was not significantly higher in mild and moderate (BI) in 2 subjects (40.0%) compared to 1 subject (20.0%) in severe (BI).

D-dimer, LDH, ferritin, and CRP Levels in COVID-19 Smoker and Non-Smoker Patients

The results of the data normality test for D-dimer, LDH, ferritin, and CRP levels in smokers and non-smokers as described in Table 4.

In Table 4, the comparison of D-dimer between smokers and non-smokers shows a significance value of 0.000 (p <0.05), significant, whereas in smokers with a median D-dimer of 1620 ng/ml, it is higher than in non-smokers with a median D-dimer of 1002.5 ng/ml.

The results of the comparison of the LDH of patients between smokers and non-smokers show a significance value of 0.160 (p >0.05), significant, where smokers' median LDH of 405.5 IU/L is lower than the median LDH of non-smokers, which is 418 IU/L.

Ferritin comparison results between smokers and non-smokers COVID-19 patients showed a significance value of 0.203 (p >0.05), so it can be interpreted that there is no significant difference in the ferritin comparison between smokers and non-smokers. A median of 886.65 ng/mL was higher than in non-smokers, with a median of 790.5 ng/mL.

The results of the comparison of CRP in smokers and non-smokers with COVID-19 patients showed a significant value of 0.000 (p <0.05), so it can be interpreted that the results of the comparison of CRP in patients between smokers and non-smokers showed a significant difference. The median CRP level in smokers was 13.8 mg/dL, higher than the median CRP in non-smokers, which was only 7.75 mg/dL.

DISCUSSION

Sociodemographic Characteristics of CSs (+) smokers based on the Brinkman Index (BI)

Sociodemographic characteristics in this study were divided into 3 groups, namely the mild, moderate, and severe Brinkman Index. Of the 55 CSs (+) smoking patients, there was a significant difference (p = 0.035). Most people between the ages of 18 and 39 have mild (27.78%), 40 to 64 years have mostly moderate (67.74%), and 65 years have mostly severe (BI) (50.0%). The Brinkman Index in CSs (+) COVID-19 patients increased with age, according to this study. It is possible that the older and the longer smoking the incidence of CSs is higher.

Based on the level of education, there was a significant difference (p = 0.021) in the Brinkman Index (BI), namely at the elementary and junior high school education levels, where the (BI) was the highest (50.0% and 33.33%). At the high school level, the majority were classified as moderate (BI) (32.26%), and those not found (BI) were severe. At the undergraduate level, most of them had mild (BI) (61.11%). From this study, it was found that the Brinkman Index in CSs (+) COVID-19 patients was getting worse in line with the low level of patient knowledge. This is not in accordance with the RISKESDAS data that, based on the level of education, the higher the level of education, the higher the amount of cigarette and tobacco consumption; however, the difference in prevalence is not significant.[13]

Based on work, it was found that CSs (+) in COVID-19 patients who worked as civil servants, lecturers, and teachers mostly had mild (BI) (11.11%), no moderate (BI), and no severe (BI). Jobs as health workers have similarities with jobs as private employees, namely mild (BI) (5.56% and 22.22%) and no severe (BI). Jobs as self-employed and traders have similarities with those of patients who are not working, students, and retirees, mostly in moderate (BI) (25.81% and 35.48%). Most of the patients who worked as laborers, farmers, or drivers had severe (BI) (66.7%). The degree of Brinkman Index may be influenced by the high mobility and social environment in which the patient works.

CSs in Smoking and Non-Smoking COVID-19 Patients

The comparison of smoker status between patients who have CSs (+) and CSs (-) shows a significance value of 0.024, so it can be interpreted that the results of the comparison of smoker status between patients who have CSs (+) and CSs (-) show a difference, which means that the incidence of CSs (+) is higher in smokers (54.5%) than non-smokers (45.5%), while in contrast, patients with CSs (-) are lower in smokers (26.3%) than non-smokers (73.7%).

These results are consistent with the previous theory that smoking is like adding fuel to the fire because smoking can upregulate the receptor angiotensin-converting enzyme-2 (ACE-2) used by SARS-CoV-2 to enter host cells so that more and more viruses enter. further increases the risk of cytokine storms, which can worsen the condition of COVID-19 patients.[3] Furthermore, these findings are consistent with previous research indicating that the value of CSs is considered positive if two biomarkers, namely serum D-dimer, ferritin, LDH, or CRP levels, have increased.[6]

CSs in Smoking COVID-19 Patients Based on the Brinkman Index

The incidence of CSs (+) was not significantly (p=0.733) higher in moderate (BI), namely 31 subjects (56.4%) compared to mild (BI), 18 subjects (32.7%), and 6 subjects (10.9%) in severe (BI). This is inconsistent with previous research that cigarette smoke induces epigenetic modifications of the bronchial epithelium, which causes metaplasia of mucus (goblet) cells, so that the more cigarettes are smoked, the more ACE2-producing goblet cells in the lungs will increase, which is the receptor used by SARS-CoV-2 to enter host cells.[14] However, in that study, there were various comorbidities, whereas in our study, we excluded all existing comorbidities, so from the results of this study, we suspect that the CSs (+) incident has actually occurred at a moderate degree.

Comparison of D-dimer, LDH, ferritin, and CRP Levels in Smoker and Non-Smoker COVID-19 Patients

The comparison of D-dimer levels between smokers and non-smokers with COVID-19 patients was significantly (p = 0.001) higher in smokers than non-smokers with COVID-19 patients (median: 1620 mg/L vs. 1002.5 mg/L). The results of these D-dimer levels are in line with previous research that indicates that increasing D-dimer levels in smokers can increase the incidence of thromboembolic coagulopathy, causing worsening in patients with confirmed COVID-19.[15] And according to the results of other studies, high D-dimer levels correlate with the severity of COVID-19. Reports of D-dimer levels vary, but the median level of D-dimer levels is around 1000 ng/Ml.[6]

The comparison of CRP levels between smoking and non-smoking COVID-19 patients revealed significantly (p = 0.001) higher levels in smokers than non-smokers (median: 13.8 mg/dl vs. 7.75 mg/dl). The results of this study are in accordance with the theory in the form of a meta-analysis test, which shows that smoking history and CRP are parameters that can be used to evaluate the severity of COVID-19[16] and another meta-analysis showed that levels were higher at >10 mg/L in smokers than non-smokers.[11]

The LDH level of smokers in COVID-19 patients was lower (405.5 ng/ml) compared to non-smokers (411.75 ng/ml), but not significantly (p = 0.160). These results are inconsistent with the literature, which suggests that smokers have increased LDH levels, which are useful for counteracting excess free radicals from the effects of smoking, so that they will increase serum antioxidant enzymes (LDH) in the blood compared to non-smokers.[9] However, the results of this study's LDH levels are in accordance with other studies where there is an increase in LDH levels > 245 U/L, which is related to the worsening of COVID-19.[17]

Ferritin levels were higher in smokers with a median of 886.65 ng/ml compared to non-smokers (790.5 ng/ml), but not significantly (p = 0.203). Although not significant, these results are in accordance with previous studies in multivariable regression analysis showing that the median ferritin level increased with smoking status, namely in former or active smokers, and increased with the number of smokers in all subgroups of patients who were categorized according to spirometry results.[18] Based on a meta-analysis of 27 laboratories, it was concluded that the level of severity can be determined from inflammatory markers, and the most prominent difference is ferritin, with levels of 423.13 ng/mL (281.41–582.85).[19]

CONCLUSION

Cytokines Storm scores (CSs) increased significantly in COVID-19 patients smokers. D-dimer and CRP levels were significantly higher in smoking COVID-19 patients compared to non-smokers. Ferritin levels were higher and LDH lower but not significant in smokers with COVID-19 patients compared to non-smokers.

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