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Systematic Review

Involvement of KL-6 Biomarker in Interstitial Lung Disease Induced by SARS-CoV-2 Infection: A Systematic Review

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Abstract: Early prognosis of severe disease and preventive actions hang around as the mainstay in managing the novel SARS-COV-2 outbreak due to the lack of robust therapeutic strategies. Krebs von den Lungen-6 (KL-6 or KL-6/MUC1) is a relatively new discovered transmembrane mucoprotein that was shown to be a good predictor of disease severity in interstitial lung diseases (ILD). We aimed to systematically research the literature in order to assess the relationship between the KL-6 biomarker and prognosis of SARS-CoV-2 infection. A literature search was performed in PubMed, Embase, and Cochrane library databases from inception to 8 March 2021. After eligibility assessment, eight studies were finally included in the present systematic review. All included studies are observational and single-center. The data gathered suggests the importance of prognostic implications of KL-6 in COVID-19 as patients with a more severe disease had significantly higher levels of KL-6 at admission. Moreover, the KL-6 biomarker was associated with COVID-19 severity, lung lesion areas on computed tomography, pulmonary fibrosis, and coagulation disorders. The association with mortality is unclear and needs further research. More extensive trials are required to prove that facile, inexpensive, and good predictors of severe outcomes, such as KL-6, could be safely integrated into the clinical decision-making in patients with COVID-19.

Keywords: interstitial lung disease; SARS-CoV-2; COVID-19; KL-6; disease severity; prognostic biomarkers

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1. Introduction

Modern medicine has provided physicians with many "prodigies" regarding the understanding and therapeutical approaches of pulmonary diseases, such as interstitial lung diseases (ILDs), idiopathic pulmonary fibrosis (IPF), or other chronic conditions with multifactorial and complex pathophysiology [1].

The novel coronavirus disease 2019 (COVID-19) is distinguished by significantly lower understanding and less efficient therapeutic strategies in severe cases. Despite the vaccination policies adopted in many countries, COVID-19 represents a global health problem with a high disease burden on worldwide healthcare systems [2]. Moreover, a paramount concern is raised around the new variants of the virus (especially B.1.1.7 and B.1.3.5) that were already spotted in several countries [3] and seemed to render the approved vaccines inefficient [4].

Therefore, due to the lack of robust therapeutic strategies, early prognosis of severe disease and preventive actions hang around as the mainstay in managing the SARS-CoV-2

outbreak [5]. As such, the identification of early markers of severe disease constitutes an urgent matter.

Pathophysiology of lung injury due to SARS-CoV-2 infection is a complex inflammatory and immunological process which leads to interstitial disease and pulmonary fibrosis [6–8]. As a consequence, the pathophysiological similarities between COVID-19 and ILD/IPF were studied [9]. The overlapping of some of the COVID-19 and ILP/IPF pathways is meaningful and essential as prognostic biomarkers of ILD and IPF may also represent valuable markers for SARS-CoV-2.

Krebs von den Lungen-6 (KL-6 or KL-6/MUC1) is a relatively new discovered high-weight transmembrane mucoprotein found on type II alveolar epithelial cells that is expressed in the blood flow, secondary to pulmonary tissue lesions [10]. KL-6 has been proposed as a biomarker in many research papers regarding ILDs, especially as a supplemental enhancer of specificity when affirming the diagnostic in cases "out of the guidelines" or as a predictor for disease severity [11]. It is also a demonstrated prognostic and diagnostic biomarker for the severity of acute respiratory distress syndrome (ARDS) as higher concentrations of circulating KL-6 ($p < 0.001$) correlate positively with peak and mean airway pressure and oxygenation index potential role in ARDS diagnosis [12]. The release of KL-6 seems to result from alveolar epithelial cell damage and destruction [13]. A recent meta-analysis observed that besides good KL-6 sensitivity (0.85, 95% CI, 0.77–0.91) and specificity (0.97, 95% CI, 0.90–0.99) for interstitial lung disease, it was also associated with mortality (HR 2.95, 95% CI, 2.45–3.55, $p = 0.032$) [10].

Therefore, we propose a legitimate question regarding the role of KL-6 in COVID-19: is KL-6 associated with worse outcomes in case of lung damage due to SARS-CoV-2 infection? We aimed to systematically research the literature to assess the relationship between the KL-6 biomarker of lung injury and patients' outcomes related to SARS-CoV-2 infection.

2. Materials and Methods

According to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) checklist, we conducted the present systematic review [14] (Table S1).

2.1. Data Sources

A literature search was performed in PubMed, Embase, and Cochrane library databases from inception to 8 March 8, 2021. The following prespecified terms were used: "KL-6", "biomarker", "lung disease", "COVID-19", "SARS-CoV-2", "outcomes", "severity", "mortality", "pulmonary fibrosis" and "prediction". The search was restricted to clinical trials published in a certain time interval, namely from 2019 to 2021.

2.2. Studies Selection

Studies were considered for inclusion in the present systematic review if they fulfilled inclusion criteria: at least 10 participants aged >18 years were included in the study; original data were reported regarding the relationship between KL-6 biomarker and outcomes of patients infected with SARS-CoV-2; outcomes during hospitalization or after discharge were investigated. Several critical exclusion criteria were set: studies available only in abstract, inability to extract data, case reports, conference papers, meta-analyses, letters, unpublished data.

2.3. Data Extraction

Two individual investigators extracted the following data from each study included in the present systematic review after full-text examination: author, year, study design, patients' age, number of patients included, number of severe cases, parameters evaluated, outcomes studied, timing. Whenever possible, results reported in clinical trials were presented as area under the curve (AUC), *p*-value, r-value, median or mean values, percentages, interquartile range (IQR), and odds ratio (OR) with the corresponding 95% confidence interval (CI). The AUC is reported as a measure of the ability of KL-6 to dis-

tinguish between severe versus non-severe COVID-19 cases. The *p*-values of the reported AUCs test the null hypothesis according to which AUC equals 0.50. The r-value represents the Pearson's coefficient of correlation between KL-6 levels in severe COVID-19 patients and other parameters known to be associated with disease severity. The IQR is used in the included studies to describe the median and the middle 50% of values for various parameter levels, including KL-6. In case of elevated levels of KL-6, the OR was used to quantify the risk of death from COVID-19.

2.4. Outcomes

We appraised the relationship between the KL-6 biomarker of pulmonary tissue injury and outcomes of patients infected with SARS-CoV-2 reported in clinical trials, including at least one of the following outcomes: pulmonary fibrosis, disease severity, mortality, dyspnea, peripheral oxygen saturation, and intensive care unit (ICU) admission. In addition, when available, we presented the discriminatory power for unfavorable outcomes as well as positive and negative prediction values.

2.5. Quality Assessment

The quality of non-randomized studies included in the systematic review was assessed using the Newcastle–Ottawa tool, designed for case–control and cohort studies. It is a star-based scale composed of three domains: selection, comparability of groups, and exposure. Furthermore, domains encompass eight essential items, and nine stars could be the maximum assigned based on study quality judgment [15].

3. Results

Our search in prespecified databases retrieved 96 references screened for duplicates, and 14 citations were excluded. An additional 61 references were excluded based on title and abstract, leaving 21 studies for full-text review. After eligibility assessment, eight studies were finally included in the present systematic review, as 13 citations were excluded because inclusion criteria were not met (Figure 1).

The included studies' design and the population's characteristics from each study are illustrated in Table 1.

All analyzed studies were observational and single-center [16–22]. Three studies were performed in Italy, [16,20,23] one—in Japan, [17] three—in China, [18,21,22], and one—in Belgium [19]. In addition, six studies were retrospective [17–19,21–23] and two trials had a prospective design [16,20]. Results reported in clinical studies are summarized in Table 2.

In one study, d'Alessandro et al. [16] reported higher KL-6 concentrations at admission for COVID-19 patients prone to more severe disease (bilateral diffuse interstitial pneumonia or focal bilateral pneumonia), compared to patients with non-severe disease course ($p = 0.0118$) and healthy controls ($p = 0.012$). Interestingly, there was no significant difference between KL-6 levels in patients with non-severe disease and healthy participants ($p = 0.5277$). In addition, KL-6 had an excellent discriminatory power between severe and non-severe cases, with an AUC of 82.4% for a cut-off value set at 406.5 U/mL. For the prespecified cut-off value, KL-6 had 83% sensitivity and 89% specificity. Additionally, the level of natural killer (NK) cells was reported to be decreased in patients with severe infection.

Similar results were reported by Awano et al. [17]. KL-6 levels at diagnosis, as well as within one week after diagnosis, were significantly higher (respectively, $p < 0.001$ and $p < 0.001$) in the case of patients with a more severe form of COVID-19. It is essential to mention that KL-6 at peak levels within one week had the best predictive power for severe disease than other biomarkers investigated (AUC = 0.95). The predictive values of KL-6 and lactate dehydrogenase (LDH) at diagnosis were similar (AUC 0.84). At a cut-off value of 371 U/mL (within one week), KL-6 had 85.7% specificity and 96.6% specificity. Other biomarkers significantly increased in patients with severe SARS-CoV-2 infection were represented by LDH and soluble interleukin-2-receptor.

Table 1. General characteristics included in present systematic review.

Author, Year	Design	Patients, No	Age Median/ Mean ± SD	Parameters Evaluated	Outcomes	Severe Cases, No	Timing
Alessandro et al., 2020	Observational, prospective, single center	22	63	KL-6 NK cells	COVID-19 severity prediction	12	At admission
Awano et al., 2020	Observational, retrospective, single center	54	46	KL-6 LDH Ferritin D-dimer sIL2-R	COVID-19 severity prediction	21	At diagnosis and within 1 week after diagnosis
Deng et al., 2021	Observational, retrospective, single center	166	48.0 (mild cases) 55.0 (severe cases)	KL-6	-COVID-19 severity prediction -Prognosis of lung injury prediction -Coagulation dysfunction -T cells subsets dysfunctions	17	From symptom onset to 6 months post-discharge
Frix et al., 2020	Observational, retrospective, single center	83 (infected patients) 70 (healthy subjects) 31 (ILD patients)	72 (infected patients) 58 (healthy subjects) 69 (ILD patients)	KL-6 LDH PLR	-Lung disease severity -Dyspnea severity -Mortality -ICU admission	36 with high KL-6 level	At admission
Scotto et al., 2021	Observational, prospective, single center	34	63	KL-6 IL-6	Unfavourable outcome (death)	32 with oxygen therapy 15 deaths	At time of enrolment and on day 7 ± day 14
Peng et al., 2021	Observational, retrospective, single center	113 (infected patients) 65 (healthy subjects)	56 (severe cases) 50 (healthy controls)	KL-6 Fibronectin	-COVID-19 severity -pulmonary fibrosis -lymphocyte count	36	At hospital admission
Xue et al., 2020	Observational, retrospective, single center	63 (infected patients) 43 (non-infected patients)	57.20 ± 14.25 (severe cases) 55.0 ± 18.84 (non-severe cases)	KL-6	-COVID-19 severity -pulmonary lesion area -oxygenation index	15	During hospitalization
Bergantini et al., 2021	Observational, retrospective, single center	24	65.2 ± 8 (severe cases) 62.2 ± 15.6 (non-severe cases)	KL-6 C-peptide CRP IL-6	COVID-19 severity	10	At admission

COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; ICU = intensive care unit; IL-6 = interleukin 6; ILD = interstitial lung disease; KL-6 = Krebs von den Lungen 6 factor; LC = lymphocyte count; LDH = lactate dehydrogenase; NK = natural killer cells; PLR = platelets/lymphocyte ratio; sIL2-R = soluble interleukin-2-receptor; WBC = white blood cells count.

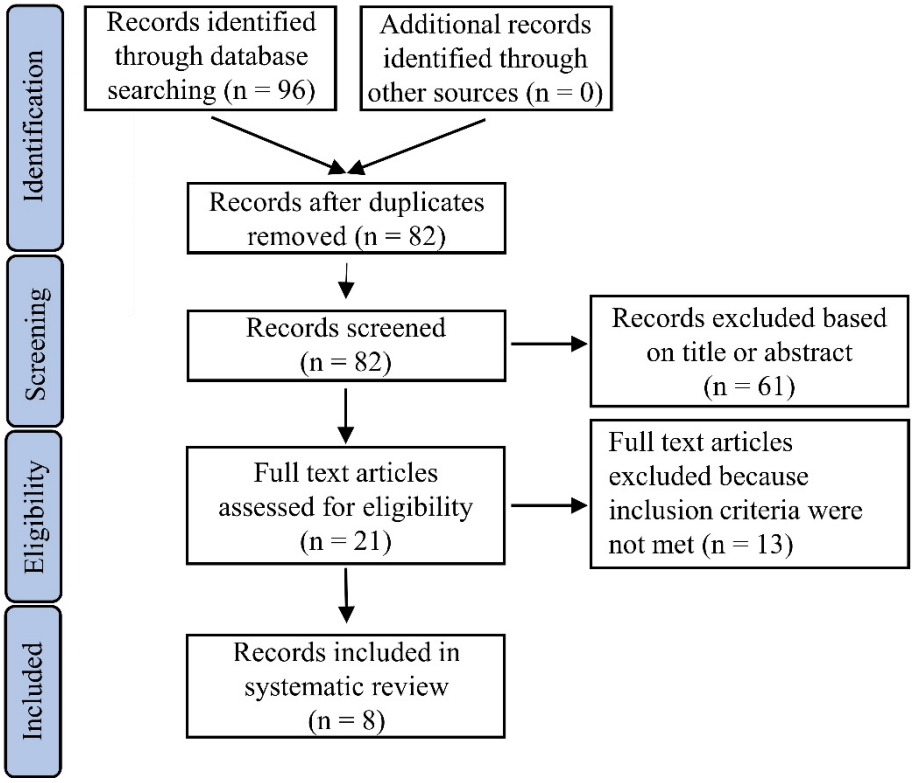

Figure 1. Flow diagram of selected studies for inclusion in the systematic review.

KL-6 levels were confirmed to be higher in patients with severe disease in another study by Deng et al. [18], though the prediction power was slightly lower from those reported in studies above (AUC = 0.793). When the cut-off value was set at 642.3 U/mL, KL-6 had a sensitivity of 75.3% and a specificity of 73.3%. At a cut-off value of 788.2 U/mL, the sensitivity was higher (86.4%), but specificity was lower (62.2%). Besides, KL-6 was found to be associated with lung lesions area on computed tomography ($p < 0.001$) and with coagulation disorders (prothrombin time, international normalized ratio, and fibrin degradation products). A relatively small number of patients with a severe form of disease ($n = 17$, 10.2%) could have led to a lower prediction value of KL-6, but it still was statistically significant.

Frix et al. [19] revealed that KL-6 levels were associated with lung disease severity, as defined by median SpO_2 at admission ($p = 0.013$). Regarding other outcomes investigated, results were discrepant, as KL-6 levels were not associated with severe dyspnea, intensive care unit admission, and mortality ($p > 0.05$). A provocative observation in this study was that KL-6 concentrations in patients with pre-existing interstitial lung disease were significantly higher than in patients with COVID-19, highlighting the importance of an individualized approach in interpreting the results.

One study included almost only patients requiring oxygen therapy at baseline ($n = 32$, 94.1%) [20]. Results reported by Scotto et al. were different from those reported in the study above, in the sense that KL-6 levels (>1000 U/mL) were significantly associated with mortality, an effect which maintained even after multivariate analysis (OR 11.29, 95% CI, 1.04–122.00). The other biomarker investigated, namely interleukin-6 (IL-6), was associated with mortality only in univariate analysis (cut-off > 100 pg/mL), an effect which was lost at multivariate analysis (OR 4.03, 95% CI, 0.39–41.78). Noteworthy, KL-6 concentration at the time of enrolment had an excellent predictive value for mortality (AUC = 0.849). Surprisingly, a more advanced age (>60 years) was not associated with death in univariate analysis (OR 1.17, 95% CI, 0.28–4.83, $p = 0.83$).

Table 2. Results reported in clinical studies.

Author, Year	Outcomes	Parameters	Results	
Alessandro et al., 2020	COVID-19 severity	KL-6, U/mL (severe vs. non-severe)	AUC 82.4% (95% CI, 62–100)	$p = 0.0129$
			1021 (IQR, 473–1909) vs. 293 (IQR, 197–362)	$p = 0.0118$
		KL-6, U/mL (non-severe vs. healthy controls)	293 (IQR, 197–362) vs. 239 (IQR, 132–371)	$p = 0.5277$
		KL-6, U/mL (severe vs. healthy controls)	1021 (IQR, 473–1909) vs. 239 (IQR, 132–371)	$p = 0.012$
		NK cells/μL (non-severe vs. severe)	AUC 78.6% (95% CI, 55–100)	$p = 0.0425$
			141 (IQR, 88–205) vs. 74 (IQR, 32–101)	$p = 0.0449$
Awano et al., 2020	COVID-19 severity	At Diagnosis		
		KL-6, U/mL (severe vs. non-severe)	AUC = 0.84	
			338 (IQR, 303–529) vs. 223 (IQR, 166–255)	$p < 0.001$
		LDH, U/L (severe vs. non-severe)	AUC = 0.84	
			356 (IQR, 293–480) vs. 208 (IQR, 169–275)	$p < 0.001$
		sIL2-R, U/mL (severe vs. non-severe)	AUC = 0.82	
			1152 (IQR, 715–1773) vs. 616 (IQR, 459–734)	$p < 0.001$
		Within one week (peak levels)		
		KL-6, U/mL (severe vs. non-severe)	AUC = 0.95	
			781 (IQR, 429–1435) vs. 234 (IQR, 194–282)	$p < 0.001$
		LDH, U/L (severe vs. non-severe)	AUC = 0.84	
			479 (IQR, 356–700) vs. 243 (IQR, 173–313)	$p < 0.001$
		sIL2-R, U/mL (severe vs. non-severe)	AUC = 0.88	
			1431 (IQR, 1126–1963) vs. 664 (IQR, 500–869)	$p < 0.001$
Deng et al., 2021	COVID-19 severity	KL-6 (mild vs. severe/critical)	AUC = 0.793 (95% CI, 0.718–0.868)	$p < 0.001$
	CT lung lesions areas	KL-6 within the previous week	N/A	$p = 0.753$
		KL-6 within the next week	$r^2 = 0.3153$	$p < 0.001$
	FDP	KL-6 (severe patients)	r = 0.641	$p = 0.001$
	INR	KL-6 (severe patients)	r = 0.517	$p = 0.001$
	PT	KL-6 (severe patients)	r = 0.512	$p = 0.001$
Frix et al., 2020	Lung disease severity	KL-6 (high level vs. low level)	Median SpO_2 = 90% vs. median SpO_2 = 94%, r = –0.271	$p = 0.013$
	Severe dyspnea	KL-6	N/A	$p = 0.585$
	ICU admission	KL-6	N/A	$p = 0.434$
	Mortality	KL-6	N/A	$p > 0.05$
Scotto et al., 2021	Death	KL-6 > 1000 U/mL	OR 11.29 (1.04–122.00)	$p < 0.05$
		KL-6 at enrolment	AUC 0.849 (95% CI, 0.702–0.996)	$p < 0.01$
		IL-6 > 100 pg/mL	OR 4.03 (0.39–41.78)	$p = 0.243$
Peng et al., 2021	COVID-19 severity	KL-6	AUC = 0.8266	$p < 0.001$
	Pulmonary fibrosis	KL-6	N/A	$p < 0.05$
		Fibronectin	N/A	$p > 0.05$
Xue et al., 2020	COVID-19 severity	KL-6, U/mL (severe vs. non-severe)	676.6 ± 506.70 vs. 241.2 ± 207.90	$p < 0.05$
	Pulmonary lesion area	KL-6	N/A	$p < 0.05$
Bergantini et al., 2021	COVID-19 severity	KL-6, U/mL (severe vs. non-severe)	903 (IQR, 333.8–1956) vs. 320 (IQR, 226.3–927.8)	$p = 0.035$
		IL-6	AUC 0.85 (95% CI, 0.79–1)	$p = 0.003$
		KL-6 + IL-6 + CRP	AUC 0.95 (95% CI, 0.86–1)	$p = 0.004$

AUC = area under the curve; CI = confidence interval; CRP = C-reactive protein; CT = computed tomography; FDP—fibrin degradation products; ICU = intensive care unit; INR = international normalized ratio; IQR = interquartile range; KL-6 = Krebs von den Lungen 6 factor; LDH = lactate dehydrogenase; NK = natural killer cells; OR = odds ratio; PT = prothrombin time; sIL2-R = soluble interleukin-2-receptor.

A similar results' direction was observed by Peng et al. [21]. Patients with severe disease had greater levels of KL-6, which had a good predictive value (AUC = 0.8266) for disease severity, even though the optimal cut-off value was lower than in the above studies (278.3 U/mL). The authors also studied the association between pulmonary fibrosis and KL-6 and observed a statistically significant relationship as patients with pulmonary fibrosis had greater KL-6 levels ($p < 0.05$). In contrast to KL-6, the association of fibronectin with pulmonary fibrosis was not statistically significant.

Xue et al. [22] confirmed that KL-6 levels were higher in patients with a severe or critical form of COVID-19 ($p < 0.05$). Also, as compared to healthy controls, patients infected with SARS-CoV-2 had higher levels of KL-6. Noteworthy, from five severe patients with a progressive aggravation of the general condition, KL-6 levels continued to increase in two of them, suggesting that KL-6 could be an early marker of the disease progression. A similar increase in KL-6 concentrations was also documented as clinically worsening in one of two patients with non-severe forms of infection. Moreover, KL-6 levels were associated with pulmonary lesion area ($p < 0.05$).

Bergantini et al. [23] also reported that KL-6 levels were higher in patients with severe disease than those with non-severe phenotypes of COVID-19. KL-6, when combined with two other markers of severity, namely IL-6 and C-reactive protein (CRP), had an exceptional discriminatory power, with AUC 0.95 (95% CI, 0.86–1), evoking the importance of an integrative approach of existing biomarkers in order to predict the course of the disease.

The quality assessment of included studies using the Newcastle–Ottawa scale is presented in Table S2. Overall, as all studies were observational, the quality estimated was fair to poor.

4. Discussion

As the SARS-CoV-2 pandemic still exerts a high pressure on health care providers, efficient patient triage to detect those with severe forms of disease or at high risk of worse outcomes is of great importance. For this purpose, various biological and imagistic markers were reported in the literature, including KL-6. This is the first systematic review addressing the relationship between KL-6 biomarker and COVID-19 outcomes, to the best of our knowledge.

High KL-6 levels are associated with worse outcomes, prognosis, and mortality in patients with interstitial lung diseases, other than SARS-CoV-2 infection [10], even in the stable states of diseases [24]. In one study, patients with idiopathic pulmonary fibrosis (IPF) and high KL-6 levels or continuous increase had a worse prognosis than those with lower KL-6 concentrations and without increase over time [25]. Although challenging in approach and a frequent misdiagnosis subject [26], IPF patients can benefit from this relatively simple monitoring method by having their KL-6 levels measured to predict an acute exacerbation with great sensitivity [27], especially during these pandemic times. All this data suggests the importance of a serial evaluation rather than a single measurement, but the predictions and outcomes can be significantly more beneficial for the patients [28]. That is why the prognostic implications of KL-6 in COVID-19 are of great interest.

One study [16] showed that KL-6 at admission was significantly increased in severe COVID-19 patients when compared to healthy subjects or those with non-severe forms, with an excellent predictive value. Those with non-severe phenotype had similar levels with healthy controls. All severe patients included in this trial were intubated and admitted to ICU. Although a small number of patients were included, these results were also confirmed by other studies. Another study [17] also documented that patients with severe SARS-CoV-2 infection had higher KL-6 values at admission. In addition to dosage at admission, KL-6 at peak levels within one week had the best predictive value for disease severity from all markers investigated. Other studies [18,19,21–23] included in the present systematic results revealed similar results, as patients with a more severe disease had significantly higher levels of KL-6.

Since KL-6 overlaps with existing pulmonary modifications, mainly in patients with chronic lung damage, KL-6 can be used as a reliable method to evaluate the extent of the lesions and, hence, the disease's progression [13] (Figure 2).

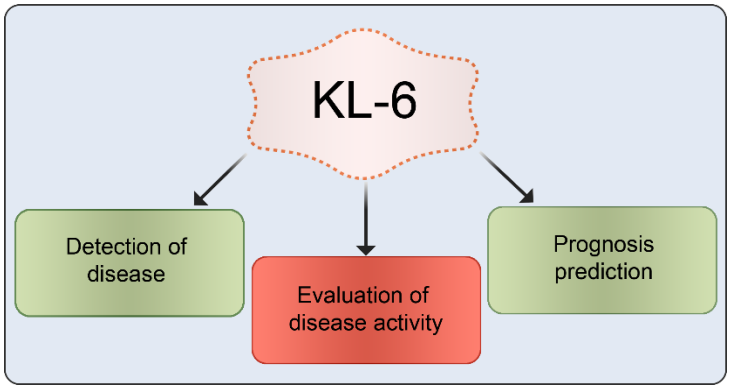

Figure 2. The three main areas of applicability of KL-6 in managing the SARS-COV-2 outbreak.

A single KL-6 measurement at admission could be a good marker of disease severity in COVID-19 patients and might be used in patients' triage to detect those requiring advanced monitoring and a more aggressive treatment strategy. Moreover, serial evaluations of KL-6 concentrations during hospitalization could identify patients with a higher risk of clinical deterioration. However, more studies are needed with larger populations in order to confirm these observations.

In addition, it is not compulsory to use KL-6 alone to predict the severity of the disease. One study [23] showed that a combination of three markers, KL-6, IL-6, and CRP, had an exceptional predictive value for COVID-19 severity with an AUC of 0.95 (95% CI, 0.86–1). More studies to investigate the importance of different clinical models, including biomarkers and imagistic signs in disease severity prediction, are warranted.

Regarding the association of KL-6 with mortality in COVID-19, research data are discordant in two studies included in our systematic review. One study [19] did not find any statistically significant association between KL-6 levels and mortality or ICU admission. However, in another study, [20] the authors observed that patients with higher KL-6 levels had a higher risk of death, an effect which maintained at multivariable analysis. Even so, the proportion of patients who died was very high (n = 15 out of n = 34), limiting the results in all-comer patients with COVID-19 who had a lower mortality rate. More studies are needed to elucidate the link between KL-6 and mortality in COVID-19 patients.

KL-6 is demonstrated to be associated with severe outcomes in interstitial diseases [29] and seems to be a reliable predictor of mortality [30]. Deng et al. [18] linked KL-6 to both lung computer tomography (CT) lesions and coagulation abnormalities (prothrombin time, international normalized ratio, and fibrin degradation products), but the results are limited by the small number of patients with a severe form of the disease included in the study. On the other hand, KL-6 levels are strongly correlated with the progression of lung lesions in rheumatoid arthritis, specifically discriminating the fibrotic from the non-fibrotic form [31].

It remains a provocative idea, if KL-6 could be used as a marker to detect patients who would benefit from anticoagulant therapy, but more trials are required. In one study [21] the authors observed that patients who developed pulmonary fibrosis at discharge had significantly higher levels of KL-6 ($p < 0.05$). Patients with severe forms of COVID-19 had signs of pulmonary fibrosis at computed tomography in 36.11% of cases. A possible clinical implication emerges from these data, in the sense that KL-6 may be used to evaluate the interstitial disease course instead of computed tomography at long-term follow-up, thus limiting the dose of radiation. However, more studies are required to confirm these results.

A problem regarding the use of KL-6 in clinical practice is represented by the fact that cut-off values used to estimate the risk of worse outcomes were different across studies

so that it is hard to establish which concentration is the best. In addition, a cut-off value that could be extrapolated to all patients does not seem appropriate, as patients with pre-existing interstitial lung disease may exhibit high baseline KL-6 values regardless of COVID-19 severity. That is why an individualized approach is required, and higher cut-off values might be used in patients with pre-existing pulmonary disease. Cut-off values of 500 U/mL seem to distinguish healthy individuals from patients suffering from interstitial lung diseases [32]. However, values over 1000 U/mL that are positively correlated with increased risk of mortality in patients with ILDs, especially IPF [33], could represent valuable information to extrapolate to COVID-19 patients that develop interstitial lung modifications with permanentizing tendency, especially prolonged ARDS [12,34].

Although KL-6 is a relatively inexpensive marker, no information is available regarding a single or serial measurement's cost-effectiveness. Thus, large clinical trials are awaited to address these issues and to suggest possible solutions.

Because the data were heterogeneous, including population, KL-6 cut-off value used, time of measurement, and clinical setting, the results of a quantitative synthesis could be misleading and were not performed.

5. Conclusions

The SARS-CoV-2 pandemic remains a serious global health problem, despite the preventive measures adopted and vaccination policies, with tremendous pressure on health care providers. Effective, fast, and integrative methods to identify patients with severe disease forms or at high risk of worse outcomes are of great importance. For this purpose, the KL-6 biomarker was associated with COVID-19 severity, lung lesion areas on computed tomography, pulmonary fibrosis, and coagulation disorders. The association with mortality is unclear and needs further research. More extensive trials are required to prove that facile, inexpensive, and good predictors of severe outcomes, such as KL-6, could be safely integrated into the clinical decision-making in patients with COVID-19.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/app11083482/s1, Table S1: Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) checklist, Table S2: Quality assessment using Newcastle-Ottawa scale.

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