Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
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EVIDENCE SUMMARY

Should LDH, CRP and Ferritin be used to guide immunotherapy in patients with COVID-19?

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RECOMMENDATION

There is insufficient evidence to recommend the use of specific cut-off values of CRP, LDH and Ferritin to guide the initiation of immunotherapy in patients with COVID-19 *(Very low quality of evidence)*.

Consensus Issues

It was noted that varying cut-off values of LDH, CRP and Ferritin to predict mortality and severity of disease were used in the studies included in this review, hence, no specific levels can be recommended to guide initiation of immunotherapy for COVID-19 patients.

Key Findings

Very low quality evidence from 25 retrospective and prospective observational studies revealed varying cut-off values of lactate dehydrogenase (LDH), C-reactive protein (CRP), and ferritin producing heterogenous effect estimates for predicting mortality, severity on admission, and disease progression in hospitalized COVID-19 patients.

Introduction

Severe COVID-19 disease is characterized by an immunologic and hyperinflammatory response known as the cytokine release syndrome (CRS), whereby elevated pro-inflammatory cytokines, such as IL-2, IL-6, IL-10, and TNF-α cause multiple organ dysfunction, and possibly death. This uncontrolled immune response serves as the basis of immunotherapy in severe to critical COVID-19 [1]. However, determining the onset of CRS is largely a clinical dilemma, as testing for the cytokines that herald it are not readily available in most institutions, and when they are, come at a high cost. Meanwhile, other markers of inflammation, such as lactate dehydrogenase (LDH), C-reactive protein (CRP), and ferritin have also been observed to be elevated in COVID-19 and, in some earlier cohort studies, were found to be associated with disease severity, progression, and mortality [2]. These are more readily available and less costly compared to the cytokines.

Current international society recommendations have utilized these inflammatory markers as guides for initiation of immunotherapy. For instance, the recommendation for initiation of tocilizumab is a CRP level of $\geq$ 75mg/L [3–6] and/or a ferritin level of $\geq$ 1000 ng/ml [7]. Serial monitoring of LDH, ferritin, and CRP were also recommended while patients are on immunotherapy [7, 8]. However, these cut-off levels were based on earlier cohort studies on patients with COVID-19 from Wuhan, China [9]. Subsequent systematic reviews and meta-analyses [10–14] have consistently revealed the value of CRP and LDH in predicting severe

outcomes in COVID-19, however, the cut-off points vary between studies, making it difficult to generalize. This evidence review seeks to determine the specific levels of LDH, CRP, and ferritin which are associated with disease severity and mortality in hospitalized COVID-19 patients, which, in turn, may be utilized as a guide for initiation of immunotherapy.

Review Methods

We searched MEDLINE through PUBMED, the Cochrane library, and the COAP Living Evidence Database last May 13, 2021, using the following search terms: "CRP" OR "C-reactive protein" OR "hsCRP" OR "ferritin" OR "ferritin" [Mesh] OR "lactate dehydrogenase" OR "LDH" AND "Mortality" OR "Mortality" [Mesh] OR "Severity" OR "Severity" [Mesh] AND COVID-19. We included studies that recruited adult hospitalized patients diagnosed with COVID-19, which reported baseline C-reactive protein (CRP), ferritin, and lactate dehydrogenase (LDH) values. Studies with the following outcomes were included: mortality and progression to more severe stages (e.g., cytokine storm, acute respiratory distress syndrome [ARDS], need for mechanical ventilation or ICU admission, shock, etc).

We excluded studies that enrolled children or adolescents, studies that had a sample size of <100 participants, as well as studies that did not control for confounders via multivariate analysis. We also excluded studies which did not report a cut-off value for a particular biomarker (i.e., with incomplete data), or that did not report an effect estimate (e.g., odds ratio, hazards ratio) for the biomarkers of interest. Regarding methods, meta-analyses, systematic reviews, and observational studies were prioritized.

We limited our search to those written in English only, but did not limit the date of publication. For studies with inaccessible full-text articles, supplementary materials, or presented data, the respective corresponding authors were contacted via e-mail.

Two independent researchers assessed the risk of bias per study using the Newcastle-Ottawa scale for cohort studies. Any disagreements were discussed between the reviewers; if no resolution was reached, this was elevated to a third, independent reviewer.

Results

Characteristics of Included Studies

A total of 530 studies were obtained from the search; their titles and abstracts were screened by two independent authors. Included studies from one rapid review [12] and four meta-analyses were also retrieved and cross-referencing was done [10, 11, 13, 15]. After application of inclusion and exclusion criteria, only 24 published studies and 1 unpublished study [16] remained for analysis (Appendix 1, Table 1). A total of 16,577 hospitalized, RT-PCR confirmed adult COVID-19 patients were recruited across the 25 studies spanning four continents: Asia (Philippines, China, Kuwait, and Japan) [15–33], Africa (Algeria) [34], North America (United States of America and Mexico), and Europe (Spain) [35], from December 2019 to August 2020. Of the 15 studies from China, nine were on patients from Wuhan [18–21, 25, 29–31, 33]. Across all studies, the lowest median age was 41 years old and the highest was 67 years old. Majority of the hospitalized patients were male. With regards to study design, 22 were retrospective cohorts [15–24, 26–33, 35–38] two were prospective cohorts [25, 34], while one was a case-control study [39]. Seventeen studies were based on data from a single center [15, 16, 18, 22–25, 28, 29, 31–35, 37, 39, 40], while eight studies were multi-center [17, 19, 21, 26, 27, 30, 36, 38].

Risk of bias assessment

Risk-of-bias was assessed using the Newcastle-Ottawa scale for cohort studies; all were of low risk of bias (overall score of 7 to 8), except for two retrospective observational studies by

Mikami et al. [36] and Yitao et al. [22], which were deemed as having high risk of bias with overall scores of 6 and 5, respectively. As in all of the included studies, there were issues on selection in that the outcome of interest is already present at baseline. . The study by Mikami et al., also had issues with the brevity of follow-up period, in that not all patients that were selected as part of the cohort developed the outcomes of interest [36]. The observational cohort by Yitao et al., also did not mention the method by which exposure and outcomes were ascertained, hence the score [22].

Summary of results of included studies

Outcome: Mortality

CRP

Fourteen studies included CRP in their investigation for independent predictors of mortality from COVID-19. Two retrospective cohort studies specifically utilized high-resolution CRP (hs-CRP) (Appendix 2, Table 2). However, in both studies, one with a cut-off of > 3 mg/L [28], and the other with a cut-off of >100 mg/L [32], elevated hs-CRP was not found to be independently associated with mortality on multivariate analysis (values not presented by their respective study authors).

The remaining twelve retrospective cohort studies which analyzed CRP levels revealed widely varied cut-off values for this particular biomarker, with minimal to no apparent trend in effect estimates (Appendix 2, Table 3) [16–19, 23, 25, 30-31, 34–36, 38]. Across all studies, CRP was significantly elevated in patients who succumbed to COVID-19 as compared to survivors of the disease. However, upon controlling for multiple covariates via multiple regression analysis, only three studies [31, 35, 38] revealed CRP as an independent predictor of mortality in COVID–19 patients, at a cut-off value of $\geq$ 6 mg/L (OR 9.72, [95%CI 3.36 - 28.11]) [31], $\geq$ 100 mg/L (HR 4.3, [95% CI 1.74,10.58]) [35] and at a cut-off of 231mg/L (OR 4.71, [95% CI 2.35-9.46]) [38]. The remaining 9 studies concluded that CRP was not an independent predictor of mortality on multivariate analysis (the results of which were not presented by the study authors) [16–19, 23, 25, 30, 34, 36].

Available odds ratios were pooled via inverse generic variance for three studies [23, 31, 38], which revealed a pooled OR of 5.91 (95% CI 3.36 to 10.40), I^2 at 0% (Appendix 3, Figure 1). Subgroup analysis was also done with CRP cut-offs of 10 mg/L, 75 mg/L, and 100 mg/L. There were two studies that presented CRP cut-offs of 6 mg/L and 8 mg/L, yielding similar forest plots. [23, 31] There was one study with a CRP cut-off above 100 mg/L, set at 231 mg/L. [38]. Pooled OR for the studies with cut-offs below 10 mg/L yielded a pooled OR of 9.19 (95% CI: 3.48 to 24.30) with an I^2 value of 0% [23, 41].

Studies which reported HR were initially pooled via a similar approach, however as the data was heterogenous (I^2=89%), the pooled data is not presented in this review.

Ferritin

Five retrospective observational studies included ferritin in their analysis (Appendix 2, Table 4). Ferritin was significantly elevated in non-survivors compared to survivors, and was likewise associated with mortality based on univariate, but not on multivariate, analysis. Only one study revealed ferritin > 834 ng/mL as an independent predictor of in-hospital mortality in COVID-19 patients with a sensitivity of 85.25% and specificity of 69.5% (OR 13.11[95% CI:4.19 to 41.02])

[34]. The four remaining studies, on the other hand, revealed non-significant results upon multivariate analysis for ferritin cut-offs of > 150 ng/mL (males) and > 248 ng/mL (females) [17], > 434 ng/mL (males) and > 278 ng/mL (females) [16], > 500 ng/mL [32], and > 300 ng/mL [21].

LDH

In the 12 retrospective observational studies, LDH was significantly elevated in the cohort of non-survivors. We attempted to pool the available data via inverse generic variance, but the resulting heterogeneity was high (I^2= 86% and 81%, for pooled adjusted OR and HR, respectively) hence we opted not to present the forest plots.

Of these, six studies [17, 19, 30, 32, 35, 38] reported LDH as an independent predictor of mortality in COVID-19 with the following cut off values (Appendix 2, Table 5): > 245 U/L (HR 5.963, 95% CI 2.029-17.529) [30], > 245 U/L (HR 1.002 [95% CI 1-1.004]) [26], > 245 U/L HR 1.003 (95% CI 1.002 – 1.004) [19], > 250 U/L (OR 8.74, 95% CI 1.98-38.5) [17], ≥ 334 U/L (HR 2.0, 95% CI 1.04-3.84) [35], > 445 U/L (OR 2.0 [95% CI 1.21 - 3.3] [32] and > 561 U/L (OR 3.03 [95% CI 1.4-6.55]) [38]. The 6 remaining studies revealed non-significant results for LDH on multivariate analysis using the following cut off values: ≥225 U/L, ≥ 227 U/L [16], >245 U/L [21], >250 U/L [18], and >440 U/L [36].

Outcome: COVID-19 severity on admission

CRP

Of the nine studies that investigated CRP as a predictor of COVID-19 severity on admission, none of the studies used hs-CRP. COVID-19 patients who presented with severe to critical disease had a significantly higher CRP level on admission, compared to patients with mild to moderate disease. Pooled data had significant heterogeneity (I^2=85%), hence the forest plot was not presented. Two studies showed that CRP is a significant predictor of COVID-19 severity on admission, with threshold levels of: >8mg/L (OR 9.09 [95% CI 1.97-41.95]) [23] and >10mg/L (OR 11.29 [95% CI 1.58 - 80.84] [15]. The rest of the studies, on the other hand, did not reveal significant results on multivariate analysis at the following CRP threshold levels: > 5mg/L [19], >10mg/L [15,24,27,36,41] > 38.55mg/L [29], and >123mg/L [34] (Appendix 2, Table 6).

Ferritin

Ferritin was also significantly elevated in severe to critical COVID-19. On multivariate analysis, however, two retrospective observational studies revealed no significant association of ferritin at a cut off level of > 200ug/L [41] and > 602 ng/L [34] with COVID-19 severity at admission among COVID-19 hospitalized patients (Appendix 2, Table 7).

LDH

Six retrospective cohort studies were included. LDH levels in severe to critical COVID-19 were likewise elevated compared to non-severe cases. Pooled data were likewise significantly heterogenous (I^2=95%), hence we opted to present the data in a tabulated format, as presented by their respective study authors (Appendix 2, Table 8). On multivariate analysis, only one study showed a significant result at cut off > 250U/L but with very wide confidence interval (OR 219.6 [95%CI 19.33 - 2494.47]) [27]. The rest did not show that LDH, using the cut-off of > 230-250 U/L [19, 24, 27, 30, 41], as independent predictor of disease severity on admission.

Outcome: Disease Progression

CRP

Four retrospective observational studies included CRP, not specified as hsCRP, in their investigation of predictors of in-hospital progression (Appendix 2, Table 9). One study revealed CRP as an independent predictor of disease progression which was further specified as: (1) predictor of progression to moderate to critical for levels of CRP ≥ 6mg/L (OR 7.44 [95% CI (3.14 - 17.64) and (2) predictor of progression to moderate to severe for levels of CRP ≥ 6mg/L (OR 2.35 [95% CI 1.47 - 3.37]) [32]. The rest did not reveal CRP as an independent predictor of in-hospital disease progression at CRP cut off levels ≥ 10 -30 mg/L [22,38,41].

Ferritin

None of the included studies investigated ferritin as a marker of disease progression in COVID-19.

LDH

Three retrospective observational studies (Appendix 2, Table 10) did not reveal LDH as an independent predictor of in-hospital progression across various threshold values of LDH: > 250 U/L [41], 500 U/L [38], and LDH > 700 U/L [38,40] on multivariate analysis (specific effect estimates not presented by study authors).

Recommendations from Other Groups

Latest recommendations from the United States National Institute of Health, Infectious Disease Society of America (April 2021), and NICE Guidelines in UK (March 2021), utilized a CRP cut-off value of > 75mg/L for initiating immunotherapy, particularly Tocilizumab. The National Institute for Infectious Diseases in Italy [8] recommended the use of ferritin, CRP and LDH for serial monitoring during infusion of immunotherapy (such as Tocilizumab) and failure to reduce levels by 50% from baseline levels warrant a second dose of therapy. The local guidelines from the Philippines last July 2020 stated the use of ferritin > 1000 ng/ml as one of the indications for initiating Tocilizumab; furthermore, they stated serial monitoring of ferritin, CRP, and LDH during therapy [7].

Research Gaps

Studies on the outcomes of immunotherapy initiated at specific levels of LDH, CRP, and ferritin, as well as the trends in the level of these biomarkers on subsequent monitoring would provide more direct evidence as to the role of these biomarkers in optimal COVID-19 management. Additionally, analyses on the levels of LDH, CRP, and ferritin at which a second dose of immunotherapy (e.g., tocilizumab) would lead to optimal outcomes should be undertaken.

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Appendix 1. Characteristics of Included Studies

Table 1. Summary of included studies

Study ID	Country	Sample size	Biomarker (cut-off)	Outcome	Effect estimate[b]
Almazeedi 2020	Kuwait	1096	CRP (>8 mg/L)	Severity, Mortality	OR
Cheng B 2020	Wuhan, China	456	CRP (>6 mg/L)	Severity, Mortality	OR
Chen 2021	Wuhan, China	635	CRP (per 1 mg/L increase above 5mg/L), LDH (per 1U/L increase)	Severity, Mortality	OR
De Vera 2021	Philippines	258	CRP (>6mg/L), Ferritin (>278 ng/mL, >434 ng/mL), LDH (>227 U/L)	Mortality	OR
Du 2020	Wuhan, China	179	CRP (>10 mg/L)	Mortality	OR
Feng 2020	China	476	CRP (>3 mg/L), LDH (>245 U/L)	Mortality	HR
Higuera-dela Tijera 2021	Mexico	166	CRP (not indicated), LDH (>700 U/L)	Severity	OR
Huang H 2020	China	125	CRP (>10 mg/L), LDH (>250 U/L)	Severity	OR
Huang R 2020	China	220	CRP (>10 mg/L), LDH (>250 U/L)	Severity	OR
Li K 2020	China	102	hsCRP (3 mg/L), LDH (>225 U/L)	Mortality	OR
Li X 2020	China	548	hsCRP (10 mg/L), LDH (>250 U/L), ferritin (>500 ng/L)	Mortality	OR
Liu 2021	Wuhan, China	122	CRP (>10 mg/L), LDH (>250 U/L), ferritin (>200 ng/L)	Severity	OR
Mikami 2021	USA	6493	CRP(>150 mg/L), LDH (>440 U/L)	Mortality	HR
Nunez 2021	Mexico	282	CRP (>20 mg/L, >30 mg/L), LDH (>500 U/L, >700 U/L)	Composite[a]	HR
Peiro 2021	Spain	196	CRP (>100mg/L), LDH (33 4U/L)	Mortality	HR
Sayah 2021	Algeria	153	CRP (>123 mg/L), Ferritin (603 ng/L)	Severity, Mortality	OR
Shang M 2021	Wuhan, China	159	CRP (>10 mg/L), LDH (>250 U/L)	Mortality	OR
Shang W 2020	Wuhan, China	443	CRP (>38.55 mg/L)	Severity	OR

Study ID	Country	Sample size	Biomarker (cut-off)	Outcome	Effect estimate[b]
Soria 2021	Philippines	2884	CRP (>3 mg/L), LDH (>250 U/L), ferritin >248 ng/mL)	Mortality	OR
Tabata 2020	Japan	107	CRP (>10 mg/L), LDH (>230 U/L)	Severity	OR
Vidal-Cevallos 2021	Mexico	377	CRP (>231 mg/L), LDH (561 U/L)	Mortality	OR
Yitao 2021	China	257	CRP (18.5 mg/L)	Severity	OR
Zhang J 2020	Wuhan, China	220	CRP (>10 mg/L), LDH (>250 U/L)	Severity	OR
Zhang X 2021	Wuhan, China	432	CRP (>10 mg/L), LDH (>245 U/L)	Mortality	HR
Zhou 2020	Wuhan, China	191	LDH (>245 U/L),ferritin (>300 ng/mL)	Mortality	OR

Legend: OR, odds ratio; HR, hazards ratio
[a]Composite outcome (ICU admission, mechanical ventilation, mortality)
[b]As reported by study authors

Appendix 2. Summary of Findings

Table 2. Association of mortality with high-resolution CRP (hs-CRP)

Outcome	Basis (sample size)	Biomarker cut off (mg/L)	Effect Estimate[a]	95% CI	Interpretation (Independent Predictor? Yes/No)
MORTALITY	**Li K 2020** n=102	>3 mg/L	Not significant on multivariate analysis (no report of adjusted OR)		No
	Li X 2020 n=158	>100 mg/L	Not significant on multivariate analysis (no report of adjusted OR)		No

[a] Effect estimates as reported by study authors

Table 3. Association of in-hospital mortality with CRP

Outcome	Basis (sample size)	Biomarker cut-off (mg/L)	Effect Estimate[a]	95% CI	Interpretation (Independent Predictor? Yes/No)
MORTALITY	**Almazeedi 2020** n=1096	>8 mg/L	OR 6.880	0.615-76.911	No
	Cheng B 2020 n=456	≥6 mg/L	OR 9.723	3.363-28.112	**Yes**
	Vidal – Cevallos 2021 n=377	> 231 mg/L	OR 4.71	2.35 – 9.46	**Yes**
	Peiro 2021 n=196	≥ 100 mg/L	HR 4.3	1.74 – 10.58	**Yes**
	Mikami 2020 n=6493	> 150 mg/L	HR 1.03	0.78 – 1.36	No
	Chen 2020 n=836	> 5 mg/L	HR 1.001	1.000 – 1.002	No
	Du 2020 n=179	>/10 mg/L	Not significant on multivariate analysis (no report of adjusted OR)		No
	Sayah 2021 n=153	> 150 mg/L	Not significant in multivariate analysis (no report of adjusted OR)		No
	Zhang X 2021 n=432	>10 mg/L	Not significant in multivariate analysis (no report of adjusted OR)		No
	Shang M 2021 n=159	> 10mg/L	Not significant in multivariate analysis (no report of adjusted OR)		No

	Soria 2021 n=2884	> 3 mg/L	Not significant in multivariate analysis (no report of adjusted OR)	No
	De Vera 2021 n=258	≥ 6 mg/L	Not significant in multivariate analysis (no report of adjusted OR)	No

[a] Effect estimates as reported by study authors

Table 4. Association of in-hospital mortality with ferritin

Outcomes	Basis (sample size)	Biomarker cut-off (g/mL)	Effect Estimate[a]	95% CI	Interpretation (Independent Predictor? Yes/No)
MORTALITY	**Sayah 2021** n=153	> 834 ng/mL	OR 13.11	4.19-41.02	**Yes**
	Soria 2020 n=2884	> 248 ng/mL (male) > 150 ng/mL (female)	Not significant in multivariate analysis (no report of adjusted OR)		No
	Zhou 2020 n=191	> 300 ng/mL	Not significant in multivariate analysis (no report of adjusted OR)		No
	De Vera 2021 n=258	> 434 ng/mL (male) > 278 ng/mL (female)	Not significant in multivariate analysis (no report of adjusted OR)		No
	Li X 2020 n=545	>500 ng/mL	Not significant in multivariate analysis (no report of adjusted OR)		No

[a] Effect estimates as reported by study authors

Table 5. Association of in-hospital mortality with LDH

Outcomes	Basis (sample size)	Biomarker cut off (U/L)	Effect Estimate[a]	95% CI	Interpretation (Independent predictor? Yes/No)
MORTALITY	**Li K 2020** n=102	>225 U/L	OR 1.01	1.005-1.015	No[b]
	De Vera 2021 n=258	>227 U/L	OR 1.0038	1.002 - 1.006	No[b]
	Soria 2021 n=2884	> 250 U/L	OR 8.74	1.98 – 38.5	**Yes**
	Li X 2020 n=545	>445 U/L	OR 2.0	1.21-3.3	**Yes**
	Vidal – Cevallos 2021 n=377	> 561 U/L	OR 3.03	1.4 – 6.55	**Yes**
	Zhang X 2021 n=432	> 245 U/L	HR 5.963	2.029 – 17.529	**Yes**
	Feng 2020 n=476	>245 U/L	HR 1.002	1-1.004	No[b]
	Peiro 2021 n=196	≥ 334 U/L	HR 2.0	1.04 – 3.84	**Yes**
	Mikami 2020 n=6493	> 440 U/L	HR 1.25	0.86 – 1.81	No
	Chen 2020 n=836	> 245 U/L	HR 1.003	1.002 – 1.004	**Yes[b]**

	Zhou 2020 n=191	≥ 245 U/L	Not significant in multivariate analysis (no report of adjusted OR)	No
	Shang M 2021 n=159	> 250 U/L	Not significant in multivariate analysis (no report of adjusted OR)	No

[a] Effect estimates as reported by study authors
[b] Considered as significant by study authors

Table 6. Association of severity at admission with CRP

Outcome	Basis (sample size)	Biomarker Cut-off (mg/L)	Effect Estimate[a]	95% CI	Interpretation (Independent predictor? Yes/No)
SEVERITY	**Almazeedi 2020** n=1096	>8 mg/L	OR 9.09	1.97-41.95	**Yes**
	Huang H 2020 n=125	>10 mg/L	OR 11.289	1.577- 80.838	**Yes[b]**
	Shang W 2020 n=443	≥38.55 mg/L	OR 1.017	1.004-1.030	No[b]
	Chen 2021 n=836	> 245 U/L	HR 1.021	0.938 – 1.110	No
	Liu 2021 n=122	≥ 10 mg/L	Not significant in multivariate analysis (no report of adjusted OR)		No
	Tabata 2020 n=104	>10 mg/L	Not significant on multivariate analysis (no report of adjusted OR)		No
	Zhang J 2020 n=663	>10 mg/L	Not significant on multivariate analysis (no report of adjusted OR)		No

	Huang R n=220	>10 mg/L	Not significant on multivariate analysis (no report of adjusted OR)	No
	Sayah 2021 n=153	> 123 mg/L	Not significant in multivariate analysis (no report of adjusted OR)	No

[a] Effect estimates as reported by study authors
[b] Considered as significant by study authors

Table 7. Association of severity on admission with ferritin

Outcomes	Basis (sample size)	Biomarker cut-off (ng/L)	Effect Estimate[a]	95% CI	Interpretation (Independent predictor? Yes/No)
SEVERITY ON ADMISSION	**Liu 2021** n= 122	> 200 ng/L	Not significant in multivariate analysis (no report of adjusted OR)		No
	Sayah 2021 n=153	> 602 ng/L	Not significant in multivariate analysis (no report of adjusted OR)		No

[a] Effect estimates as reported by study authors

Table 8. Association of severity on admission with LDH

Outcomes	Basis (sample size)	Biomarker cut-off (U/L)	Effect Estimate[a]	95% CI	Interpretation (Independent predictor? Yes/No)
SEVERITY ON ADMISSION	**Liu 2021** n=122	> 250 U/L	OR 1.007	1.002 – 1.011	No[b]
	Huang H 2020 n=125	>250 U/L	OR 219.608	19.332-2494.74	Yes
	Chen	>245 U/L	OR 1.008	1.003 – 1.013	No[b]

	(without comorbidities) n=201				
	Chen (with comorbidities) n=635	>245 U/L	OR 1.006	1.004 – 1.008	No[b]
	Tabata 2020 n=104	>230 U/L	Not significant in univariate and multivariate analysis (no report of adjusted OR)		No
	Zhang J 2020 n=663	>250 U/L	Not significant in multivariate analysis (no report of adjusted OR)		No
	Huang R 2020 n=220	>250 U/L	Not significant in multivariate analysis (no report of adjusted OR)		No

[a] Effect estimates as reported by study authors
[b] Considered as significant by study authors

Table 9. Association of disease progression with CRP

OUTCOME	Basis (sample size)	Biomarker Cut-off (mg/L)	Effect Estimate[a]	95% CI	Interpretation (Independent Predictor? Yes/No)
Progression from moderate to critical	**Cheng B** n=456	≥6 mg/L	OR 7.444	3.142-17.636	**Yes**
Progression from moderate to severe	**Cheng B** n=456	≥6 mg/L	OR 2.346	1.474-3.733	**Yes**
Composite	**Liu 2021** n=122	≥ 10 mg/L	OR 1.019	1.004 – 1.035	No[b]

Clinical type worsened + death					
Composite **ICU + mortality**	**Yitao 2021** n=257	≥ 18.45 mg/L	OR 1.037	1.008 – 1.066	No[b]
Composite **Need for IMV, ICU, Death**	**Nunez 2021** n=282	≥20 mg/L	HR 1.26	0.93 – 1.71	No
		≥30 mg/L	HR 1.51	0.89 – 2.55	

[a] Effect estimates as reported by study authors
[b] Considered as significant by study authors

Table 10. Association of disease progression with LDH

Outcomes	Basis	Biomarker cut off	Effect Estimate[a]	95% CI	Interpretation (Independent Predictor? Yes/No)
In hospital composite progression (Clinical Type Worsening + Death)	**Liu et al** n= 122	≥ 250 U/L	Not significant in multivariate analysis (no report of adjusted OR)		No
IN HOSPITAL PROGRESSION (MV, ICU, Death)	**Nunez 2021** n= 282	≥ 500 U/L	HR 1.21	0.87 – 1.71	No
		≥ 700 U/L	HR 1.32	0.94 – 1.85	
Need for IMV	**Higuera dela Tijera 2021** n= 166	≥ 700 U/L	OR 2.7	0.8 – 9.9	No

[a] Effect estimates as reported by study authors

Appendix 3. Forest Plots

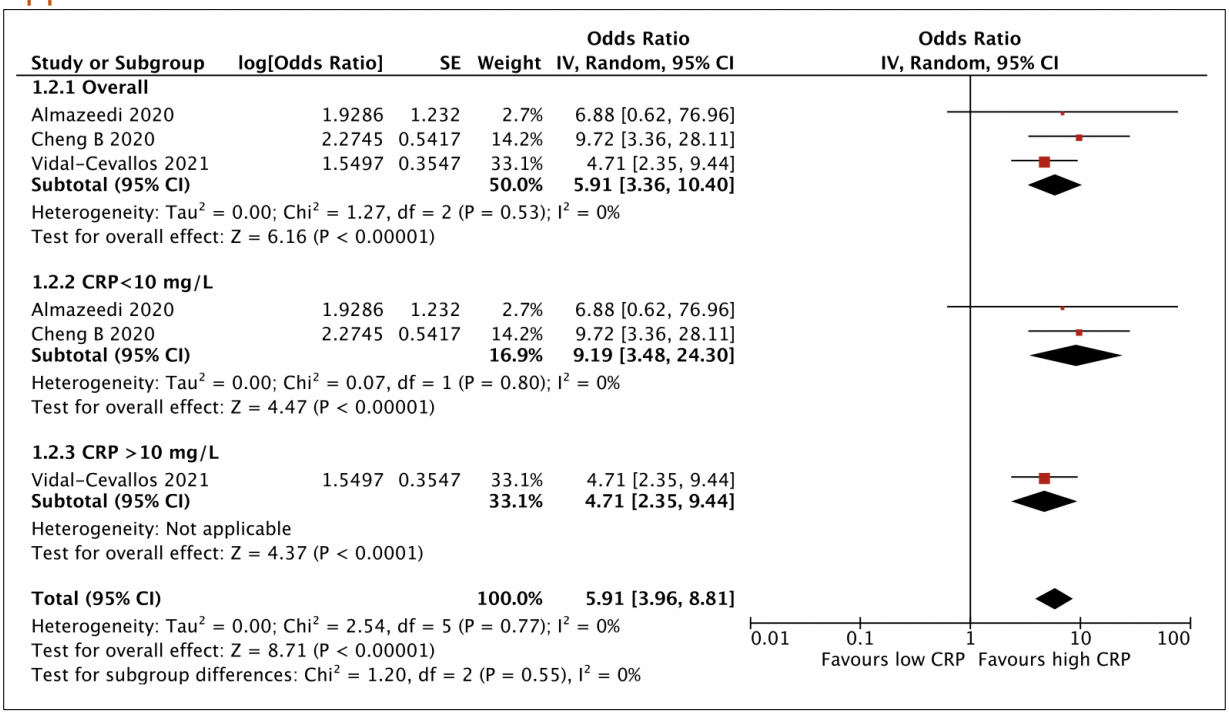

Figure 1. Association of mortality with elevated CRP (pooled odds ratios via inverse generic variance). Subgroup analysis was done for groups with a CRP cut-off value above and below 10 mg/L. CRP cut-off values of 75 mg/L and 100 mg/L would yield the same forest plot.

Appendix 4. GRADE Evidence Profile

No. of studies	Certainty assessment						impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
CRP and COVID-19 severity on admission									
9	observational studies	not serious	serious	not serious	serious	none	Risk of bias score of the studies is 7-8 via NOS, thus, rating them as having low risk of bias. However, only 2 studies [Almazeedi, Huang H] had significant results in multivariate analysis and the others did not report values to properly assess inconsistency. Also, despite resulting into independent predictors of severity on admission, the corresponding confidence intervals are very wide leading to significant imprecision. Also, the CRP cut off levels vary from (>5mg/L to > 123mg/L) that may lead to heterogeneity of results.	⊕⊕◯◯ LOW	IMPORTANT
LDH and COVID-19 severity on admission									
7	observational studies	not serious	serious	not serious	serious	none	Risk of bias score vis NOS of the studies is 7-8, thus, rating them as having low risk of bias. However, only 1 study [Huang, H] had significant result in multivariate analysis and the other half (6/12) did not report effect estimates, to properly assess inconsistency. Also, despite resulting into an independent predictor of severity on admission, the corresponding confidence interval is very wide leading to significant imprecision.	⊕⊕◯◯ LOW	IMPORTANT
Ferritin and COVID 19 severity on admission									
2	observational studies	not serious	serious	not serious	serious	none	Risk of bias score of the studies via NOS is 7-8, thus, having low risk of bias. However, the results of the 2 studies showed that Ferritin was not a significant predictor of COVID-19 severity on admission after multivariate analysis. The effect estimates were not reported, thus, inconsistency and imprecision cannot be properly assessed. Also, the cut off levels vary (>200ng/ml and > 602ng/ml) which may lead to heterogeneity of results.	⊕⊕◯◯ LOW	IMPORTANT
CRP and COVID-19 in-hospital progression (composite outcome of progression of severity classification, ICU admission, need for mechanical ventilation, and death)									
4	observational studies	serious	serious	not serious	serious	none	Risk of bias of the studies is 5-8 via NOS, rating 3 as having low risk of bias and 1 as having high risk of bias [Yitao]. Only 1 study had significant result in multivariate analysis [Cheng B]. Also, the cut off values vary >6mg/L, >10mg/L, >20mg/L, and >30mg/L.	⊕◯◯◯ VERY LOW	IMPORTANT

LDH and COVID-19 in-hospital progression (composite outcome of progression of severity classification, ICU admission, need for mechanical ventilation and death)									
3	observational studies	not serious	serious	not serious	serious	none	Risk of bias of the studies is 7-8 via NOS, rating them as having low risk of bias. None of the studies resulted to LDH as a significant predictor of COVID-19 in- hospital progression. Also, the cut off values used vary (>250 U/L, >500 U/L, >700 U/L) which may lead to heterogeneity of results.	⊕⊕◯◯ LOW	IMPORTANT
CRP and in-hospital mortality									
14	observational studies	serious	serious	not serious	serious	none	Risk of bias score of the studies is 6-8 via NOS, rating one as having high risk of bias [Mikami] and the rest as having low risk of bias. Only 3 studies had significant results in multivariate analysis but with wide confidence intervals leading to significant imprecision. More than half did not report effect estimates in multivariate analysis to properly assess inconsistency. Also, the cut off levels vary leading to significant heterogeneity (>3mg/L to >150mg/L).	⊕◯◯◯ VERY LOW	IMPORTANT
Ferritin and in-hospital mortality									
5	observational studies	not serious	serious	not serious	serious	none	Risk of bias score via NOS of the studies is 8, rating them as having low risk of bias. Only one study reported significant result in multivariate analysis [Sayah], making Ferritin as independent predictor of in-hospital mortality at cut off level of 824 ng/ml, OR 13.11 (95% CI 4.19 to 41.02). However, the rest of the studies did not report effect estimates in multivariate analysis and their cut off levels vary (>248ng/ml, >300ng/ml, >434ng/ml, >500ng/ml) that may lead to heterogeneity of results.	⊕⊕◯◯ LOW	IMPORTANT
LDH and in-hospital mortality									
12	observational studies	serious	serious	not serious	serious	none	Risk of bias score via NOS is 6-8, rating one study [Mikami], as having high risk of bias, and the rest with low risk of bias. Six studies reported LDH as a significant predictor of in-hospital mortality but with varying cut off levels (>225 to >561 U/L) and effect estimate reporting (HR and OR). The rest did not report effect estimates in multivariate analysis. Wide confidence interval and absence of effect estimates in half of the studies may lead to imprecise results and inadequate assessment of inconsistency.	⊕◯◯◯ VERY LOW	

Appendix 5. Risk of Bias Assessment

Table 11. Newcastle-Ottawa Scale for Cohort Studies

	Mikami 2021	Chen 2021	Peiro 2021	Zhang 2021	Vidal-Cevallos 2021	Soria 2021	Higuera-dela Tijera 2021	Sayah 2021	Shang 2021	Liu 2021	Nunez 2021	Yitao 2021	Zhou 2020	De Vera 2021
Representativeness of the exposed cohort														
Selection of the non-exposed cohort														
Ascertainment of exposure														
Demonstration that the outcome of interest was not present at the start of the study														
Comparability of cohorts on the basis of design or analysis														
Assessment of outcome														
Was follow-up long enough for outcomes to occur?														
Adequacy of follow-up of cohorts														
OVERALL SCORE	**6**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**7**	**8**	**5**	**8**	**8**

(cont.)

	Almazeedi 2020	Cheng B 2020	Feng 2020	Shang W 2020	Huang H 2020	Li K 2020	Li X 2020	Tabata 2020	Zhang J 2020	Huang R 2020	Du 2020
Representativeness of the exposed cohort											
Selection of the non-exposed cohort											
Ascertainment of exposure											
Demonstration that the outcome of interest was not present at the start of the study											
Comparability of cohorts on the basis of design or analysis											
Assessment of outcome											
Was follow-up long enough for outcomes to occur?											
Adequacy of follow-up of cohorts											
OVERALL SCORE	**7**	**7**	**8**	**8**	**8**	**8**	**8**	**7**	**7**	**7**	**8**

***Legends: Blue (y*es or done equivalent to 1 star*); yellow (no or not done or not stated equivalent to no star)*

For overall score: green (low risk of bias); red (high risk of bias)