Best Evidence Topic Report 8

Titel:

Welke parameters worden best opgevolgd bij het monitoren van patiënten met een matig ernstige Covid-19 infectie?

Auteurs:

Lotte Michielsen[1], Clara Merckx[1], Trudy Bekkering[2], Jan Verbakel[3], Marc Van Nuland[3]

Affiliatie:

1. student 3e Master Geneeskunde, KU Leuven
2. CEBAM, het Belgisch Centrum voor Evidence-Based Medicine, Leuven
3. Academisch Centrum voor Huisartsgeneeskunde, KU Leuven

Antwoord op klinische vraag:

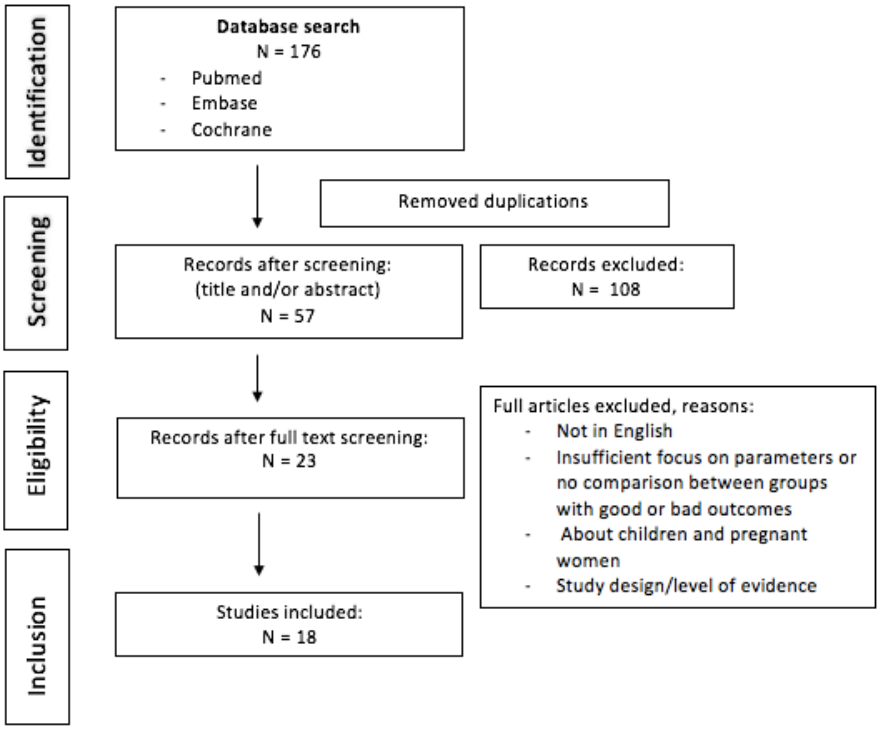
Vitale parameters (koorts, tachypnee, zuurstofsaturatie) en bepaalde labowaarden (CRP, lymfocyten, Il-6, D-dimeren) blijken gecorreleerd te zijn met ernst van infectie en kunnen van prognostische waarde zijn in follow up van patiënten met een Covid-19 infectie. Enige reserve in onze beoordeling is gepast, gezien de uitgebreide risico's op bias en heterogeneïteit.

Disclaimer:

Deze rapporten zijn ontwikkeld volgens de methode van de Best Evidence Topics, kortweg bestBETs. Een bestBET beoogt een antwoord te geven op een specifieke klinische vraag, geformuleerd op basis van het op dit ogenblik best beschikbare bewijs. Omwille van de beperkte beschikbaarheid van wetenschappelijk bewijs voor COVID-19 topics, worden ook studies van lagere kwaliteit gebruikt. BestBETs bevatten geen aanbevelingen. Studenten 3e Master geneeskunde van de KU Leuven werkten deze topics uit onder begeleiding van twee docenten, waarna ze volgens een vast stramien een eindrapport opstellen. Voor de validatie van deze rapporten, konden we beroep doen op de expertise van CEBAM, die de rapporten rigoreus toetste aan vooropgestelde kwaliteitscriteria.

Best Evidence Topic Report

Title	***Welke parameters worden best opgevolgd bij het monitoren van patiënten met een matig ernstige Covid-19 infectie?***
Report by	Lotte Michielsen & Clara Merckx (studenten geneeskunde)
Search checked by	Prof. Dr. Marc Van Nuland
Clinical scenario	De onderzoekspopulatie bestaat uit patiënten met een matig ernstige Covid-19 infectie. Binnen deze populatie wordt bekeken welke parameters een ernstigere outcome kunnen voorspellen.
Answerable question (PICO/PIRT/PEO / …)	P = patiënten met een matig ernstige Covid-19 infectie. I = monitoring van bepaalde (objectieve) parameters zoals vitale parameters en laboresultaten C = vergelijking tussen minder ernstige en ernstige infectie O = genezing of ziekteprogressie
Search terms	**Pubmed:** ((((((((((((((Oxymetrie) OR Blood Gas Analysis) OR Heart Rate) OR Respiratory Rate) OR Arterial Pressure) OR Body Temperature) OR Fever) OR C-Reactive Protein) OR Lymphopenia) OR Lymphocyte Count) OR Leukopenia) OR L-Lactate Dehydrogenase) OR Lactate Dehydrogenase 5) OR Blood Sedimentation)) AND covid-19) *NB: wanneer de MeSH-termen in verband met Outcome "Mortality" OR "Intensive care" OR "Severity of Illness Index" OR "Treatment Outcome" werden geassocieerd, verkregen we te weinig artikels.* **Embase:** (('covid 19') AND ('medical parameters' OR (body AND temperature) OR fever OR 'c reactive protein' OR 'hematological parameters' OR lymphocytopenia OR leukopenia OR 'leukocyte count' OR 'lactate dehydrogenase blood level' OR 'blood gas analysis' OR 'blood gas parameters')) *NB: wanneer de Emtree-termen in verband met Outcome "Mortality" OR "Intensive care" OR "Severity of Illness Index" OR "Treatment Outcome" werden geassocieerd, verkregen we te weinig artikels.* **Cochrane:** corona virus OR covid 19 *NB: dit leverde twee artikels op die niet relevant waren voor onze studie*
Search date	18/03/2020
Search outcome	176 papers Inclusiecriteria:

	- Studies die de outcome van Covid-19 infectie bij niet-zwangere volwassenen bekijken in functie van meetbare parameters - Cijfermatige rapportage van parameters - Level of evidence: minstens observationeel study design - Engelstalige artikels, volledig beschikbaar
Relevant papers	18 papers
Flow chart	

Evidence table*

AUTHOR, DATE, COUNTRY	STUDY TYPE (EVIDENCE LEVEL)	MAIN RISKS OF BIAS	PATIENT CHARACTERISTICS	INTERVENTION	COMPARISON	KEY OUTCOMES IN RELATION TO RELEVANT PARAMETERS
Li LQ, Huang T, Wang YQ et al. 2020 Mar 12. China(1)	Meta-analysis	small number (10) of included studies, data analysis limited due to heterogeneity	1994 hospitalized COVID-19 patients	in-hospital care & data-analysis	/	Among 1994 patients, 88.5% showed fever. The results of the clinical examination showed that lymphocytopenia (64.5%), increase of CRP (44.3%), increase of LDH (28.3%), and leukocytopenia (29.4%) were common clinical presentations. Given the heterogeneity in lab result values among different studies, no relevant indicators for severity of disease could be withheld.
Lippi, Plebani, Michael Henry. 2020 Mar 13. Italy(2)	Meta-analysis	variable definition of disease severity among studies, different cut-offs for thrombocytopenia	1779 hospitalized COVID-19 patients	in-hospital care & data-analysis	non-severe (1380) vs severe (399) cases	The pooled results of the nine studies revealed that the platelet count was significantly lower in patients with more severe COVID-19 (WMD -31x10^9/L; 95% CI, -35 to - 29x10^9/L). A low platelet count was associated with over fivefold enhanced risk of severe COVID-19. The heterogeneity was high (I^2, 92%; $p<0.001$).
Huang C, Wang Y, Li X, et al. 2020 Feb 15. China(3)	Observational study (prospective analysis)	small sample size, possible selection bias	41 hospitalized COVID-19 patients	in-hospital care & data-analysis	non-ICU (28) vs ICU (13) patients	Patients admitted to ICU had a significant higher respiratory rate (8 (62%) vs 4 (14%) >24 breaths/min) and systolic pressure (145·0 (123·0–167·0) vs 122·0 (118·5–129·5)) than non-ICU patients. Pro-thrombin time (12·2 (11·2–13·4) vs 10·7 (9·8–12·1)), D-dimer level (2·4 (0·6–14·4) vs 0·5 (0·3–0·8)), white blood cell count (11·3 (5·8–12·1) vs 5·7 (3·1–7·6)), neutrophil count (10·6 (5·0–11·8) vs 4·4 (2·0–6·1)) and lactate dehydrogenase (400·0 (323·0–578·0) vs 281·0 (233·0–357·0)) on admission were significantly higher in ICU patients than non-ICU patients. Lymphocyte count (0·4 (0·2–0·8)

						vs 1·0 (0·7–1·1)) and albumin levels (27·9 (26·3–30·9) vs 34·7 (30·2–36·5)) were significantly lower in ICU patients compared to non-ICU patients. Comparison between ICU and non-ICU patients showed that plasma concentrations of IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A , and TNFα were higher in ICU patients than non-ICU patients. A significant higher number of organ failure parameters and death was reported in ICU patients.
Wang D, Hu B, Hu C, et al. 2020 Feb 7. China(4)	Observational study (retrospective analysis)	small sample size, incomplete follow-up of patient outcomes, possible selection bias	138 hospitalized COVID-19 patients	in-hospital care & data-analysis	non-critically ill (102) vs critically ill (36) patients	There were numerous statistically significant differences in laboratory findings between patients admitted to the ICU and those not admitted to the ICU, including higher white blood cell count (6.6 (3.6-9.8) vs (4.3 (3.3-5.4)) and neutrophil counts (4.6 (2.6-7.9) vs 2.7 (1.9-3.9)), as well as higher levels of D-dimer (414 (191-1324) vs 166 (101-285), creatine kinase (18 (12-35) vs 13 (10-14)), and creatine (80 (66-106) vs 71 (58-84)). All of the patients received oxygen therapy; however only the ICU patients received oxygen via other ways than nasal canulae (p<000.1): 4 (11.1%) received high-flow oxygen therapy, 15 (41.7%) received non-invasive ventilation, and 17 (47.2%) received invasive ventilation (4 were switched to extracorporeal membrane oxygenation).
Chaomin W, Xiaoyan C, Yanping C, Jia'an X, et al. 2020 Mar 13. China(5)	Observational study (retrospective analysis)	possible selection bias, incomplete follow up of patient outcomes	201 hospitalized COVID-19 patients	in-hospital care & data-analysis	patients who developed ARDS (84) vs those who did not (117)	In bivariate Cox regression analysis, risk factors associated with the development of ARDS and progression from ARDS to death included neutrophilia (HR, 1.14; 95% CI, 1.09-1.19; and HR, 1.08; 95% CI, 1.01-1.17, respectively), and organ and

						coagulation dysfunction (e.g., higher lactate dehydrogenase [HR, 1.61; 95% CI, 1.44-1.79; and HR, 1.30; 95% CI, 1.11-1.52, respectively] and D-dimer [HR, 1.03; 95% CI, 1.01-1.04; and HR, 1.02; 95% CI, 1.01-1.04, respectively]). High fever (39 °C) was associated with higher likelihood of ARDS development (HR, 1.77; 95% CI, 1.11-2.84), but lower likelihood of death (HR, 0.41; 95% CI, 0.21-0.82). For patients with ARDS who died, the value of liver damage indices (total bilirubin [difference, 2.60; 95% CI, 0.30-5.20; P = .03]), renal dysfunction indices (urea [difference, 1.50 mM; 95% CI, 0.50-2.70; P = .004]), inflammation related indices (IL-6 [difference, 3.88; 95% CI, 2.20-6.13; P < .001]), and coagulation function indices (D-dimer [difference, 2.10 μg/mL; 95% CI, 0.89-5.27; P = .001]) were significantly elevated compared with patients with ARDS who survived.
Young BE, Xiang S, Kalimuddin S et al. 2020 Mar 3. Singapore(6)	Observational study (retrospective analysis)	small sample size, possible selection bias, limited sample collection and baseline data	18 hospitalized COVID-19 patients	in-hospital care & data-analysis	patients requiring oxygen (sat<92%) (6) vs patients not requiring oxygen (12)	Lymphopenia (<1.1 ×109/L) was present in 7 of 16 patients (39%), elevated C-reactive protein level (>20 mg/L) in 6 of 16 patients (38%) ([the 6 that required oxygen], while kidney function remained normal. Fever occurred in 13 of 16 patients (72%) [6/6 patients requiring oxygen vs 7/12 patients not requiring oxygen]. In the current study, 6 of 18 patients (33%) experienced oxygen desaturation to 92% or less, hence they were supported with supplemental oxygen. Two individuals (11%) required admission to the intensive care unit because of increasing supplemental oxygen requirements, and 1 (6%) required mechanical ventilation.

Mo P, Xing Y, Xiao Y, Deng L et al. 2020 Mar 16. China(7)	Observational study (retrospective analysis)	possible selection bias, incomplete follow up of patient outcomes	155 hospitalized COVID-19 patients	in-hospital care & data-analysis	refractory patients (85) vs non-refractory patients (75)	Compared with non-refractory patients, refractory patients had a higher level of neutrophils (P=0.017), AST (P=0.004), LDH (P=0.017) and C-reactive protein (CRP, P=0.001); and lower level of platelets (P=0.049) and albumin (P=0.001). Refractory patients had lower incidence of fever (P=0.012), but higher levels of maximum temperature among fever cases (P=0.005).Of the 155 patients, 102 patients (65.8%) received oxygen, and 36 (23.2%) with mechanical ventilation. Compared with general patients, refractory patients were more likely to receive oxygen (P<0.001) and mechanical ventilation (P<0.001).
Wang Z, Yang B, Li Q, Wen L et al. 2020 Mar 16. China(8)	Observational study (retrospective analysis)	small simple size, possible selection bias, incomplete follow up of patient outcomes	69 hospitalized COVID-19 patients	in-hospital care & data-analysis	patients with SpO2 < 90% (14) vs SpO2 ≥ 90% (55)	Compared with the SpO2≥90% group, patients of the SpO2<90% group tend to show higher frequency of fever: fever at onset of illness: 47(85%) in the SpO2≥90% group vs 13(93%) in the SpO2<90% group (p = 0.674); fever on day 10 from onset of illness: 21(38%) in the SpO2≥90% group vs 9(64%) in the SpO2<90% group (p = 0.079). Patients of the SpO2<90% group showed higher frequency of lymphopenia than those of the SpO2≥90% group (11 [79%] of 14 patients vs 17 [32%] of 53 patients, p=0.002). Also, the increase in neutrophils was significantly different between the 2 groups, with median neutrophil count 2.16 (IQR 1.60-2.70) in the SpO2≥90% group vs 5.24 (IQR 2.90-6.44) in the SpO2<90% (p < 0.001). In terms of inflammation indicators, many patients showed increased lactate dehydrogenase (25 [41%] of 61 patients, median LDH level was 207.00 (IQR 181.00-274.00) in the

						SpO2≥90% group vs 517.50 (IQR 267.00-549.00) in the SpO2<90% (p = 0.001)); c reactive protein (42 [67%] of 63 patients, median CRP level was 11.30 (IQR 6.53-26.30) in the SpO2≥90% group vs 81.55 (IQR 48.85-105.90) in the SpO2<90% (p < 0.001)); and erythrocyte sedimentation rate (30 [52%] of 58 patients, median ESR level was 17.00 (IQR 7.00-25.00) in the SpO2≥90% group vs 30.00 (IQR 27.00-49.00) in the SpO2<90% (p = 0.001)) on admission. The increase in AST was significantly different between the 2 groups, with median AST 26.00 (IQR 21.00-39.00) in the SpO2≥90% group vs 40.50 (IQR 24.00-62.00) in the SpO2<90% (p = 0.03). The IL6 and IL10 levels in plasma exceeded the upper limit of normal value in both the SpO2≥90% group and the SpO2<90% group but were significantly higher in the SpO2<90% group. 43/67 patients required oxygen support: 31(56.4%) in the SpO2≥90% group vs 12(100.0%) in the SpO2<90% group (p = 0.003). All 5 deaths occurred in the SpO2<90% group, resulting in an 41.7% mortality in that group (5/12).
Li K, Wu J, Wu F, et al. 2020 Feb 29. China(9)	Observational study (retrospective analysis)	small sample size, possible selection bias, incomplete follow up of patient outcomes	83 hospitalized COVID-19 patients	in-hospital care & data-analysis	mild (58) vs severe/critical (25)	Compared with the ordinary patients, severe/critical patients had significant higher body temperature (38.0[0.9] vs 37.6[0.6]). No significant differences of heart rate, respiratory rate and arterial pressure were found between the two groups. Compared with the ordinary patients, the severe/critical patients had increased neutrophil ratio (64% vs 15.5%), C-reactive protein (89.20 [IQR 47.88-134.64] vs 9.59 [IQR 2.07-29.89]) and

						procalcitonin, while decreased lymphocyte ratio (13.20 [IQR 6.27] vs 23.78 [IQR 8.72]) and lymphocyte count (0.70 [IQR 0.44-0.95] vs 1.23 [IQR 0.93-1.42]). White blood cell count and neutrophil count were numerically increased in severe/critical group, but the difference did not reach statistical significance. The oxyhaemoglobin saturation of the severe/critical group was significantly lower than that of the ordinary patients (95.10 [IQR 92.90-97.45] vs 97.00 [IQR 96.00-98.00]).
Wu J, Wu X, Zeng W, et al. 2020 March. China(10)	Observational study (retrospective analysis)	small sample size, possible selection bias, incomplete follow up of patient outcomes	80 hospitalized COVID-19 patients	in-hospital care & data-analysis	/	the Pulmonary Inflammation value was significantly correlated with the values of lymphocyte count, monocyte count, C-reactive protein, procalcitonin and body temperature ($p<0.05$). The correlation coefficient values were -0.260, -0.258, 0.373, 0.273, 0.287, 0.544 respectively. Regarding the laboratory data, the median leukocyte count was 5.40 (IQR: 4.20-6.95), lymphocyte count was 1.15 (IQR: 0.76-1.40); The median C-reactive protein was 12.39 (IQR: 2.71-50.60) and the procalcitonin was 0.04 (IQR: 0.03-0.07);
Xiong Y, Sun D, Liu Y, et al. 2020 March 3. China(11)	Observational study (retrospective analysis)	small sample size, possible selection bias, possible subjectivity in CT score quantification, incomplete follow up of patient outcomes	42 hospitalized COVID-19 patients, patients needed to have an initial and follow up CT scan	in-hospital care & data-analysis	/	The C-reactive protein, erythrocyte sedimentation rate and lactate dehydrogenase showed significantly positive correlation with the severity of pneumonia assessed on initial CT (R range 0.36-0.75, $p<0.05$). The highest temperature and the severity of opacifications assessed on initial CT were significantly related to the progression of opacifications on follow-up CT ($p<0.001$-0.04). Fever increased the risk of progression in the opacification severity

						score during follow-up by 3.64 times (regression coefficient B=3.64, p=0.04). Patients who had a high temperature of 38.1-39.0℃ was associated with 4 times higher progression in the opacification severity score, compared to those who had a normal temperature of <37.3℃ (B=4.15, p=0.02). There was a trend observed between rising CRP, rising LDH, lower lymphocyte count and worsening CT scores on follow-up CT scan, but no statistical correlation was obtained.
Zhang J, Dong X, Cao Y, et al. 2020 Feb 18. China(12)	Observational study (retrospective analysis)	small sample size, possible selection bias, incomplete follow-up of patient outcomes	140 hospitalized COVID-19 patients	in-hospital care & data-analysis	non-severe (82) vs severe (58) cases	In severe cases higher median values of leukocyte count (5.3 vs 4.5, P = 0.014), D-dimer (0.4 vs 0.2, P < 0.001), CRP (47.6 vs 28.7, P < 0.001), PCT (0.1 vs 0.05, P < 0.001), and lower lymphocyte percentage (median, 0.7 vs 0.8, P = 0.048) were found compared to non-severe cases.
Xu Y, Dong J, An W, et al. 2020 March 6. China(13)	Observational study (retrospective analysis)	small sample size, possible selection bias, no statistical analysis performed, incomplete follow up of patient outcomes	50 hospitalized COVID-19 patients	in-hospital care & data-analysis	mild (9) vs moderate (28) vs severe & critically severe (13) cases	No statistical analysis was performed on parameters. 49 (98%) patients had normal or slightly reduced leukocyte count, 14 (28%) had decreased counts of lymphocytes, and 26 (52%) patients had increased C-reactive protein.
Chen J, Qi T, Liu L, Ling Y, Qian Z, et al. 2020 Mar 11. China(14)	Observational study (retrospective analysis)	possible selection bias, limited statistical analysis performed, incomplete follow up of patient outcomes	249 hospitalized COVID-19 patients	in-hospital care & data-analysis	non-ICU (227) vs ICU (22) patients	Patients who were transferred to intensive care units (ICU) had significantly longer duration of fever as compared to those not in ICU (31 days vS 9 days after onset of symptoms, respectively, P<0.0001). In univariate analysis, high levels of white blood cell count, lymphocyte cell count, CRP, lactate dehydrogenase (LDH); low levels of albumin, estimated glomerular filtration rate and CD4 T cells count were all associated with the development of

						ARDS. In multivariate logistical analysis CD4 T cell counts (OR=0.55 per 100 cells/ul increase) was independently associated with ICU admission. For our patients who stayed in ICU, elevated IL 6 levels had been observed (data not shown).
Tian S, Hu N, Lou J, et al. 2020 March 2. China(15)	Observational study (retrospective analysis)	weak definition of 'severe'*, possible selection bias, incomplete follow-up of patient outcomes	262 hospitalized COVID-19 patients	in-hospital care & data-analysis	non-severe (216) vs severe (46) cases	No trend was observed regarding fever/height of temperature between severe and non-severe cases. Respiratory rate was slightly higher in severe cases but not statistically relevant.
Liu Y, Yang Y, Zhang C, et al. 2020 Mar 6. China.(16)	Observational study (retrospective analysis)	small sample size, incomplete follow up of patient outcomes	12 hospitalized COVID-19 patients	in-hospital care & data-analysis	/	Decrease in albumin and in percentage of lymphocytes were significantly correlated with infected 2019-nCoV viral load (r = 0.717 and p = 0.01 & r = 0.717 and p = 0.01 resp), as well as increase in percentage of neutrophils (r = -0.529 and p = 0.05). We found albumin, lymphocytes, neutrophils, LDH, and CRP were highly linked to lung injury Murray score. The amount of viral load, as well as the lung injury Murray score and PaO2/FiO2 ratio, may very well predict the disease severity, showing the AUC of ROC: 0.976 AND 0.984 and 0.938 resp. Among the biochemical indexes, the AUC of ROC for the infection and tissue damage indicators, albumin, CRP, and LDH were 1, 0.938, and 0.844, respectively, and may also be potential predictors of disease severity. The AUCs for lymphocyte count and the percentage of lymphocytes and neutrophils were 1, 0.844, and 0.812, respectively, and thus may also predict disease severity.
Liu K, Fang YY, Deng Y, et al. 2020	Observational study	small sample size, possible selection bias, no statistical	137 hospitalized COVID-19 patients	in-hospital care & data-analysis	/	No statistical analysis was performed on parameters. Major initial symptoms included fever (112/137, 81.8%). Nearly

Feb 7. China(17)	(retrospective analysis)	analysis performed, incomplete follow up of patient outcomes				80% of the patients had normal or decreased white blood cell counts, and 72.3% (99/137) had lymphocytopenia.
Liu W, Tao Z-W, Wang L, et al. 2020 Feb 28. China(18)	Observational study (retrospective analysis)	small sample size, possible selection bias, incomplete follow up of patient outcomes	78 hospitalized COVID-19 patients, patients needed to be hospitalized for over 2 weeks	in-hospital care & data-analysis	improvement/stabilization group (67) vs progression group (11)	The maximum body temperature at admission was significantly higher in the progression group than in the improvement/stabilization group (38.2 [37.8, 38.6] vs. 37.5 [37.0, 38.4], U=2.057, P =0.027). Moreover, the proportion of patients with respiratory failure (54.5% vs. 20.9%, chi^2=5.611, P=0.028) and with increased respiratory rate (34 [18, 48] vs. 24 [16, 60] breaths/min, U=4.030, P=0.004) was were significantly higher in the progression group than in the improvement/stabilization group. There were no significant differences in blood oxygen saturation, or heart rate between the two groups (both P > 0.05). C-reactive protein was significantly elevated in the progression group compared to the improvement/stabilization group (38.9 [14.3, 64.8] vs. 10.6 [1.9, 33.1], U=1.315, P=0.024). Albumin was significantly lower in the progression group than in the improvement/stabilization group (36.62±6.60 vs. 41.27±4.55, U =2.843, P =0.006).

**Gesorteerd volgens aflopend evidentieniveau gebaseerd op studietype, impact factor van het tijdschrift van publicatie en grootte van de studiepopulatie.Afkortingen worden weergegeven in het addendum.*

Main results

	PARAMETERS	AANTAL STUDIES MET STATISTISCH SIGNIFICANTE BEVINDINGEN	AANTAL STUDIES MET NIET-SIGNIFICANTE BEVINDINGEN ALS BELANGRIJKSTE RESULTATEN
1) KLINISCHE PARAMETERS	1. Koorts	8(5–7,9–11,14,18)	3(1,8,17)
	2. Ademhalingsritme versneld	2(3,18)	1(15)
	3. Pols versneld	0	1(18)
	4. Bloeddruk gestegen	1(3)	0
2) INFECTIEPARAMETERS	1. CRP stijging	10(6–12,14,16,18)	2(1,13)
	2. Leukocytose	4(3,4,12,14)	1(9)
	3. Leukocytopenie	1(4)	3(1,13,17)
	4. Lymfocytopenie	6(3,8–10,12,16)	5(1,6,11,13,17)
	5. Lymfocytose	1(14)	0
	6. LDH stijging	7(3,5,7,8,11,14,16)	1(1)
	7. Neutrofielen stijging	6(3–5,7,8,16)	1(9)
	8. ESR stijging	2(8,11)	0
	9. Procalcitonine stijging	3(10,12,17)	0
3) IMMUNITEITSPARAMETERS	1. IL-2 stijging	1(3)	0
	2. IL-6 stijging	2(5,8)	1(14)
	3. IL-7 stijging	1(3)	0
	4. IL-10 stijging	2(3,8)	0
	5. GCSF stijging	1(3)	0
	6. IP-10 stijging	1(3)	0
	7. MCP-1 stijging	1(3)	0
	8. MIP1A stijging	1(3)	0
	9. TNF-alpha stijging	1(3)	0
	10. CD4 daling	1(14)	0
4) BLOEDSTOLLINGSPARAMETERS	1. Thrombocytopenie	2(2,7)	0
	2. D-dimeren gestegen	4(3–5,12)	0
	3. Prothrombine tijd stijging	1(3)	0
5) ORGAANPARAMETERS	1. eGFR daling	1(14)	0
	2. Creatinine stijging	1(4)	0
	3. Ureum stijging	1(5)	0
	4. AST stijging	2(7,8)	0
	5. Totaal bilirubine stijging	1(5)	0
	6. Albumine daling	5(3,7,14,16,18)	0
	7. CK stijging	1(4)	0
6) ZUURSTOFPARAMETERS	1. Zuurstofsaturatie daling (pulse oxymetrie)	1(8)	2(6,15)
	2. Oxyhemoglobine saturatie daling	1(9)	0
	3. Definitie van ‘severe’: respiratory distress with RR > 30 times/minutes AND/OR oxygen saturation at rest < 93% AND/OR PaO2/FiO2 < 300 mmHg	0	3(12,13,18)
	4. Zuurstofnood	2(4,8)	3(5,7,17)

	5. PaO2/FiO2 daling	1(16)	1(7)
	6. Zuurstof via zuurstofbril	1(4)	3(3,5,16)
	7. Zuurstof via niet-invasieve ventilatie	1(4)	2(3,5)
	8. Invasieve mechanische ventilatie	1(4)	5(3,5–7,16)
	9. Invasieve ventilatie met ECMO	1(4)	2(3,5)
	10. Murray Score gestegen	1(16)	0

Uit verschillende studies komt naar boven dat bepaalde kwantitatief meetbare klinische en biochemische parameters gerelateerd zijn aan de ernst van de infectie.

Klinisch trad voornamelijk koorts naar de voorgrond als een belangrijke parameter. Koorts werd in 11 van de 18 studies opgevolgd, waarvan in 8 studies hogere temperaturen significant meer werden gezien bij de ernstig zieke patiënten. Verder zag men in 2 onderzoeken een significant hoger ademhalingsritme bij patiënten met en ongunstig verloop van de infectie.

De biochemische parameters werden onderverdeeld in infectieparameters, immuniteitsparameters, bloedstollingsparameters en orgaanparameters.
Bij de infectieparameters was een stijging van CRP duidelijk geassocieerd met ernst van het ziektebeeld. Deze werd in 12 studies vermeld, waarvan 10 studies een statistische significantie aantoonden. Ook lymfocytopenie werd vaak gezien bij patiënten met een Covid-19 infectie en bleek een belangrijke aantoner van ernst. Het lymfocyten aantal bleek bij 6 onderzoeken significant lager te zijn bij de ernstig zieke groep en werd nog bij 5 andere studies vermeldt als passend bij een Covid-19 infectie. Verder merkten we een discordantie in de onderzoeken wat betreft de leukocyten. In 5 studies zag men leukocytose met in 4 studies significante verschillen in het nadeel van de ernstig zieke groep, in 4 studies zag men leukocytopenie. In deze laatste 4 studies kon echter maar één studie een statistische significantie aantonen. In 7 studies meldde men een significant stijging van de neutrofielen bij patiënten met een ernstigere infectie. Dit gold ook voor een stijging van LDH, welke in 7 studies significant hoger was bij patiënten met een ernstiger verloop. Een stijging van procalcitonine met significant hogere waarden bij patiënten van de ernstig zieke groep werd gezien in 3 studies.
Wanneer we keken naar immuniteitsparameters, zagen we bij 3 studies een hoger IL-6 in vergelijking met patiënten met een milder verloop van de Covid-19 infectie. Een hogere IL-6 titer zou gecorreleerd zijn met sterfte.
Bij de bloedstollingsparameters viel een stijging van de D-dimeren op. In 4 van de onderzoeken vond men significant hogere waarden van de D-dimeren bij patiënten die er ernstiger aan toe waren. Daarnaast includeerden we een meta-analyse die specifiek focuste op trombocytopenie (2), wat een belangrijke risicofactor zou zijn voor het ontwikkelen van een ernstige infectie.
Om orgaanschade te evalueren werd gekeken naar verschillende parameters met betrekking tot de verschillende orgaansystemen. Hier viel vooral een daling in albumine op: in 5 studies werd een lager albumine gezien bij patiënten met een minder gunstige verloop.

Qua weergave van zuurstofparameters was er een zeer grote heterogeniteit tussen de onderzoeken. In 14 van de 18 studies werden zuurstofparameters weergegeven, hetzij door middel van zuurstof saturatie (pulse oxymetrie of arteriële meting), hetzij door weergave van de patiënten noden voor verschillende manieren van respiratoire ondersteuning.

Risks of bias

De belangrijkste risico's op bias zijn: 1) kleine sample size waardoor statistische significantie soms met enige reserve moet beoordeeld worden; 2) potentiële selectiebias door onderzoekers (vaak patiënten uit slechts 1 ziekenhuis, enkel gehospitaliseerde patiënten, enkel patiënten met positieve PCR, …); 3) zelden volledige follow up van klinische uitkomsten bij patiënten.

Heterogeneity

Tot de 18 geïncludeerde studies behoren 2 (eerder kleine) meta-analyse, één prospectieve observationele en 15 retrospectieve observationele studies. Bij 13 van de 18 artikels werd een vergelijking gemaakt tussen mildere en ernstigere Covid-19 infecties. De definitie van 'ernstig' was meestal verschillend van studie tot studie, maar had globaal gezien betrekking op patiënten die respiratoir meer ondersteuning nodig hadden en/of opgenomen moesten worden op ICU. In één studie werd een zeer zwakke definitie van 'ernstig' gebruikt(15): alle patiënten die zuurstofnood hadden, werden als ernstig geklasseerd. Dit is wellicht de reden dat deze studie geen significante verschillen kon weerhouden. In de andere 5 artikels werd ernst van het ziektebeeld niet gebruikt als parameter, maar werden klinische en/of biochemische parameters vergeleken met beeldvormingsresultaten en/of gebeurde er louter observatie van de kliniek zonder correlatie met patiënten uitkomsten. De verschillende studies onderzochten een grote verscheidenheid aan parameters. Daarbij gebruikten ze verschillende uitkomstmaten om hun bevindingen te rapporteren. Het gebruik van verschillende definities, het onderzoeken van verschillende parameters en het rapporteren op verschillende manieren maakte dat we een heterogene groep van studies hadden om mee aan de slag te gaan.

Clinical bottom line

Vitale parameters en bepaalde labowaarden blijken gecorreleerd te zijn met ernst van infectie en kunnen van prognostische waarde zijn in follow up van patiënten met een Covid-19 infectie. De belangrijkste prognostische parameters waren koorts, CRP-stijging, lymfocytopenie, LDH-stijging, gestegen aantal neutrofielen, IL-6 en IL-10 stijging, gestegen D-dimeren en een daling van albumine Enige reserve in onze beoordeling is gepast, cfr. de uitgebreide 'risks of bias' en heterogeneity hierboven vermeld.

References

1. Li L, Huang T, Wang Y, Wang Z, Liang Y. 2019 novel coronavirus patients' clinical characteristics, discharge rate and fatality rate of meta-analysis. JAMA Intern Med. 2020;(3):0–2.
2. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. Clin Chim Acta. 2020;
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506.
4. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061–9.
5. Chaomin W, Xiaoyan C, Yanping C, Xia J, Xing Z, Sha X. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020;1–10.
6. Young B, Xiang S, Kalimuddin S, Low J, Tan S, Loh J, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. JAMA. 2020;1–7.
7. Mo P, Xing Y, Xiao Y, Deng L, Zhao Q, Xiong Y, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. Clin Infect Dis. 2020;
8. Wang Z, Yang B, Li Q, Wen L. Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China. Clin Infect Dis. 2020;
9. Li K, Wu J, Wu F, Guo D, Chen L, Fang Z, et al. The Clinical and Chest CT Features Associated with Severe and Critical COVID-19 Pneumonia. Invest Radiol. 2020;published ahead of print.
10. Wu J, Wu X, Zeng W, Guo D, Fang Z, Chen L, et al. Chest CT Findings in Patients with Corona Virus Disease 2019 and its Relationship with Clinical Features. Invest Radiol. 2020;published.
11. Xiong Y, Sun D, Liu Y, Fan Y, Zhao L, Li X, et al. Clinical and High-Resolution CT Features of the COVID-19 Infection : Comparison of the Initial and Follow-up Changes. Invest Radiol. 2020;published.
12. Zhang J, Dong X, Cao Y, Yuan Y, Yang Y, Yan Y, et al. Clinical characteristics of 140 patients infected with SARS- CoV-2 in Wuhan , China. Eur J Allergy Clin Immunol. 2020;published ahead of print.
13. Xu Y, Dong J, An W, Lv X, Yin X, Zhang J-Z, et al. Clinical and computed tomographic imaging features of novel coronavirus pneumonia caused by SARS-CoV-2. J Infect. 2020;published ahead of print.
14. Chen J, Qi T, Liu L, Ling Y, Qian Z, Li T. Clinical progression of patients with COVID-19 in Shanghai, China. J Infect. 2020;
15. Tian S, Hu N, Lou J, Chen K, Kang X, Xiang Z, et al. Characteristics of COVID-19 infection in Beijing. J Infect. 2020;published ahead of print.
16. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci. 2020;63(3):364–74.
17. Liu K, Fang Y, Deng Y, Liu W, Wang M, Ma J, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J (Engl). 2020;0.
18. Liu W, Tao Z-W, Wang L, Yuan M-L, Liu K, Zhou L, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J (Engl). 2020;published ahead of print.

Addendum: afkortingen

ALB	albumin
ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC	area under the curve
CRP	c-reactive protein
ESR	erythrocytes sedimentation rate
GCSF	granulocyte colony-stimulating facto
HR	hazard ratio
ICU	intensive care unit
IL-10	interleukine 10
IL-6	interleukine 6
IL-7	interleukine 7
IP10	interferon-γ-inducible protein 10
IQR	interquartile range
LDH	lactate dehydrogenase
LYM	lymphocytes
MCP1	monocyte chemoattractant protein 1
MIP1A	macrophage inflammatory protein 1-alpha
NEU	neutrophils
OR	odds ratio
p	p-value
r	spearmann coefficient
ROC	receiver operating characteristics
SpO2	oxygen saturation
TNFα	tumor necrosis factor alpha