Agency for Health Technology Assessment and Tariff System

Department of Healthcare Services

Corticosteroids in treatment of COVID-19 – a rapid review

Analytical analysis performed by the AOTMiT

06/08/2020

SUMMARY

The objective of this analysis is to evaluate the efficacy and safety profile of glucocorticoids (GCs) as adjuvant therapy in COVID-19 patients as compared to the standard of care (assessment in terms of outcomes analysed in primary studies identified in the course of the conducted systematic review, along with an assessment of the relevance of results and the reliability level of scientific evidence).

The document collates results of primary and secondary studies on the use of glucocorticoids in treatment of COVID-19 identified in the course of the conducted systematic review (date of search: 27-28/07/2020). In total, 20 studies met the predefined inclusion criteria for the review – 16 primary studies and 4 secondary studies. Among the primary studies 2 experimental, 1 quasi-experimental and 13 observational (retrospective cohort) studies were included.

Of the identified reports, the most reliable one is RECOVERY – a randomised, open-label clinical trial conducted in 176 sites in the United Kingdom. The published results of the RECOVERY study support the implementation of dexamethasone therapy in the population of patients requiring respiratory support. Publicly available data confirm a particular clinical benefit in patients requiring invasive mechanical ventilation or oxygen therapy. **The use of dexamethasone reduces the mortality risk (assessed within 28 days of randomisation) in patients undergoing mechanical ventilation and those receiving oxygen therapy by 35% and 20%, respectively.** The results also indicate a greater likelihood of a patient being discharged within 28 days if dexamethasone is used, compared to the control arm. **Authors of the RECOVERY study indicate that the therapeutic effects are observed in particular in patients with symptoms persisting longer than 7 days.** However, no health benefits of dexamethasone used in the population of patients not requiring respiratory support have been reported (no statistically significant differences). **Authors of the study emphasise that it cannot be excluded that the use of dexamethasone in this patient population may increase the risk of an unfavourable course of COVID-19.**

The following document also summarises the results of other primary and secondary studies identified in the review of the scientific reports for corticosteroids used in COVID-19. It should be noted that the described primary studies (Fadel 2020, Wang 2020, Wu 2020a, Wu 2020b, Fernandez-Cruz 2020, Albani 2020, Bani-Sadr 2020, Feng 2020, Shang 2020, Lu 2020, Majmundar 2020, Li 2020, Zhou 2020, Sanz Herrero 2020) are reports with a lower level of reliability (cohort studies, retrospective studies, 1 quasi-experimental study), while Corral 2020 is an experimental study burdened with methodological limitations (partial randomisation). The methodological limitations of the above-mentioned studies influencing the uncertainty of the obtained results should also be taken into consideration.

The results of Corral 2020 indicate a statistically significant benefit of methylprednisolone (MTP) in comparison to the standard of care (SoC) in terms of the composite outcome – in-hospital death from any cause, deterioration of health resulting in the patient's transfer to the intensive care unit (ICU), respiratory failure resulting in the need for implementing invasive ventilation – a 45% risk reduction (ITT: (RR=0.55 (95%CI: [0.33; 0.91]; NNT=7)).

Methylprednisolone was used as part of corticosteroid therapy in 4 identified observational studies; in 1 study methylprednisolone was used as an adjuvant therapy to tocilizumab (Sanz Herrero 2020). Statistically significant differences in favour of MTP versus SoC were reported for:

- death rates – Fadel 2020 and Wu 2020a;
- need to implement mechanical ventilation – Fadel 2020;
- mean length of hospitalisation (8 vs 5 days) – Fadel 2020;
- transfer to the intensive care unit from the general ward – Fadel 2020;
- composite outcome – transfer to the ICU from the general ward, deterioration of respiratory failure requiring mechanical ventilation, or in-hospital death from any cause – Fadel 2020;

An increase in the risk of transferring a patient to the intensive care unit or death as a result of the use of glucocorticoids was reported in Wang 2020. It should be noted, however, that the results of the study are subject to significant uncertainty (statistically significant differences in the baseline patient

characteristics were reported – in the corticosteroid arm, a higher percentage of patients in severe condition, out of all 55 patients in severe condition, 42 received corticosteroids; small sample size; pre-print publication).

In the 10 observational studies included in the review presenting results for glucocorticoids without analysing a specific drug (the studies used methylprednisolone, dexamethasone, prednisolone or hydrocortisone in specific, equivalent doses), the results in terms of reducing the mortality risk, to compare the efficacy of glucocorticoids versus SoC in COVID-19, are ambiguous – statistically significant differences in favour of GCs versus the lack of GCs/SoC were reported in terms of the reduction of the risk of in-hospital deaths (Fernandez-Cruz 2020) and the reduction of the overall mortality risk (Fernandez-Cruz 2020, Bani-Sadr 2020). An increase in the mortality risk in the GCs arm was reported in Wu 2020b and Zhou 2020; in Li 2020, an increase in the mortality risk during hospitalisation was observed in the arm of patients using high doses of GCs. Nonetheless, it should be pointed out that the statistically significantly longer hospitalisation time observed in 4 studies in patients using glucocorticoids may be related to the tendency towards more frequent use of glucocorticoids in patients with more severe COVID-19 – no data are available to compare the baseline patient characteristics of patients in the test and control arms.

The identified secondary studies: Gangopadhyay 2020, Lu 2020, Ye 2020, Singh 2020) also analyse the results of lower-quality studies (cohort, retrospective), only the latest review – Singh 2020 – made references to the results of the RECOVERY randomised trial.

Results of the Gangopadhyay 2020 meta-analysis suggest lack of statistically significant differences with regard to the mortality risk in critical COVID-19 patients in whom GCs were used, compared to patients not subjected to such treatment. Authors of the paper state that corticosteroids should be used in patients with COVID-19 and critical illness-related corticosteroid insufficiency (CIRCI). The use of GCs should also be considered in patients with acute respiratory distress syndrome (ARDS). Authors of Lu 2020, a systematic review and meta-analysis, state that corticosteroids increase the risk of death in patients with mild COVID-19. No association between corticosteroid therapy and mortality in severely symptomatic patients was found. Authors of Ye 2020 have concluded that the use of corticosteroids can reduce the risk of death and decrease the need for mechanical ventilation in COVID-19 patients with ARDS (low-quality evidence). Singh 2020 indicated that it is difficult to draw firm conclusions on the therapeutic benefits of corticosteroids based on the available observational studies. However, attention should be paid to RECOVERY, a study in which the use of dexamethasone in severe patients allowed to obtain significantly better results than in the control arm. At the same time, authors of the paper indicated that, in order to draw firm conclusions on the effectiveness of corticosteroids in COVID-19 treatment, confirmation of the RECOVERY results in subsequent, methodologically correct clinical trials is crucial.

1. OBJECTIVE

The objective of this analysis is to evaluate the efficacy and safety profile of glucocorticoids (GCs) as adjuvant therapy in COVID-19 patients as compared to the standard of care (SoC) (assessment in terms of outcomes analysed in primary studies identified in the course of the conducted systematic review, along with an assessment of the relevance of results and the reliability level of scientific evidence).

2. METHODOLOGY

This document collates results of primary and secondary studies identified in a systematic review of scientific publications on corticosteroid treatment in COVID-19.

The systematic review of medical information databases was carried out – PubMed by Medline and EMBASE (databases searched for version 1.0 of the Recommendations in Covid-19 on 21/04/2020; update 27-28/07/2020). In order to identify papers that have not yet been published in the above-mentioned databases, a database of pre-print publications – *www.medrxiv.org* – was searched with the search period limited to 01/07–28/07/2020. Resources of the Covid-19 database were also used (www.covid19.aotm.gov.pl).

An appendix to this document presents the search strategy adopted in the review (Table 25).

Detailed criteria for including primary and secondary studies into the review are presented in the table below.

Table 1. Criteria for including primary and secondary studies into the review

Inclusion criteria for PICO	
Population	COVID-19 patients (general population or patient subpopulation)
Intervention	Glucocorticoids
Comparator	Other therapeutic treatment/conservative treatment/standard of care
Outcomes	Not identified – all outcomes for efficacy and safety profile assessment
Type of included studies	• Controlled experimental study or experimental single-arm study; • Observational studies with control group: prospective or retrospective (retrospective studies with a minimum of 50 people in the intervention arm); • Case studies and case series in the absence of scientific evidence characterised by a higher reliability level; • Registries covering >1000 patients; • Systematic reviews with a meta-analysis (inclusion of the most recent secondary studies covering the largest number of studies, exclusion of works with primary studies included in previously published works). *Systematic reviews without a meta-analysis were excluded when they included the primary studies included in this review.*

Levels of scientific evidence applied in this assessment were proposed in agreement with the Steering Committee which supervises works on the Polish COVID-19 recommendations, to determine the reliability level of the obtained results (Table 3). A grading system of the clinical trials' results was also used, taking into account the type of the analysed outcomes (clinical /surrogate outcome) and the extent of the effect (demonstrating statistically significant differences in favour of the test or control arm) (Table 2).

Table 2. Relevance of the primary study result

Statistically significant differences in favour of the intervention – clinical outcome
Statistically significant differences in favour of the intervention – surrogate outcome
Lack of statistically significant differences between study arms
Statistically significant differences in favour of the control arm – surrogate outcome
Statistically significant differences in favour of the control arm – clinical outcome

Table 3. Evidence level [1]

Level	Description
A	• Results of >1 correctly designed RCTs, high result reliability (representative sample, ITT, blinding, correct randomisation method); • Meta-analysis of correctly designed RCTs; • Results of ≥1 correctly designed RCT(s), supplemented by data from high quality registries;
B	• Correctly designed RCT, high result reliability (representative sample, ITT, blinding, correct randomisation method)
C	• RCT with few (≤2) methodological limitations (lack of blinding, small sample, limitations of randomisation method, modified ITT (mITT))
D	• Correctly designed non-randomised controlled trial, • Correctly designed prospective cohort study, • Correctly designed registry, • Meta-analysis of the above-mentioned primary studies.
E	• Randomised or non-randomised clinical trials with numerous (>2) methodological limitations (lack of blinding, small sample, incorrect randomisation method, no ITT), • Prospective observational studies with numerous methodological limitations, retrospective controlled studies
F	• Uncontrolled experimental studies, case series
G	• Case studies

[1] Presentation of adopted reliability levels based on the ACC/AHA approach (2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, accessed online: https://www.ahajournals.org/doi/full/10.1161/CIR.0000000000000678)

3. REVIEW RESULTS

As part of the conducted search, the following scientific papers on the efficacy of glucocorticoids in COVID-19 were found:

- 16 primary studies:
  - 2 RCTs – Horby 2020 (RECOVERY)[1] and Corral 2020[2],
  - 1 quasi-experimental study - Fadel 2020[3],
  - 13 retrospective studies (Wang 2020[4], Wu 2020a[5], Wu 2020b[6], Fernandez-Cruz 2020[7], Albani 2020[8], Bani-Sadr 2020[9], Feng 2020[10], Shang 2020[11], Lu 2020[12], Majmundar 2020[13], Li 2020[14], Zhou 2020[15], Sanz Herrero 2020[16]).

Secondary studies were also identified – including systematic reviews with a meta-analysis (Gangopadhyay 2020[17], Lu 2020[18], Ye 2020[19]) and without a meta-analysis (Singh 2020[20]). At the same time, it should be underlined that not all primary studies included in the identified systematic reviews meet inclusion criteria to the systematic review conducted by the AOTMiT.

3.1. Primary studies

Table 4 collates primary studies found as part of the systematic review of medical information databases (search date: 27-28/07/2020). Descriptions of the methodology and study results are presented in the tables constituting the appendix to the document.

Table 4. Summary of identified primary studies on the efficacy and safety profile of glucocorticoids in COVID-19

No.	Study	Test arm	Control arm	Types of analysed outcomes	Reliability level
1.	**Horby 2020 (RECOVERY)**	DEX	SoC	Death, hospital discharge, need for mechanical ventilation	**C**
2.	**Corral 2020**	MTP	SoC	Death, transfer to the ICU, need for mechanical ventilation	**E**
3.	**Fadel 2020**	MTP	SoC	Death, length of hospitalisation, transfer to the ICU, need for mechanical ventilation	**E**
4.	**Wang 2020**	MTP	SoC	Death, transfer to the ICU	**E**
5.	**Wu 2020a**	MTP	SoC	Death	**E**
6.	**Wu 2020b**	GCs	SoC	Death, length of hospitalisation, progression to critical state	**E**
7.	**Fernandez-Cruz 2020**	GCs	SoC	Death during hospitalisation	**E**
8.	**Albani 2020**	GCS	SoC	Death, admission to the ICU	**E**
9.	**Bani-Sadr 2020**	GCs	SoC	Mortality ratio, rate of admissions and/or deaths before admission to the ICU	**E**
10.	**Feng 2020**	GCs	SoC	Death, length of hospitalisation, hospital discharge, disease progression (need for mechanical ventilation or death)	**E**
11.	**Shang 2020**	GCs	SoC	Length of hospitalisation	**E**
12.	**Zhou 2020**	GCs	SoC	Death/survival of patients	**E**
13.	**Lu 2020**	GCs	SoC	Death	**E**
14.	**Majmundar 2020**	GCs	SoC	Death, length of hospitalisation, hospital discharge, need for intubation, transfer to the ICU, compound outcome, transfer to the ICU, intubation or death	**E**
15.	**Li 2020**	GCs	SoC	Death during hospitalisation	**E**
16.	**Sanz Herrero 2020**	MTP+TOC+ SoC	Tocilizumab + SoC	Death, length of hospitalisation, transfer to the ICU, time to virus clearance	**E**

GCs – glucocorticoids; SoC – Standard of Care); LPV/RTV – lopinavir/ritonavir; DEX – dexamethasone; MTP – methylprednisolone; TOC – tocilizumab; ICU – Intensive Care Unit

3.1.1.Randomised trials

3.1.1.1. RECOVERY

RECOVERY (*Randomised Evaluation of COVid-19 thERapY*) is a randomised, open-label clinical trial conducted in 176 sites in the United Kingdom. Over 11,500 hospitalised patients were included in the study and assigned to the following study arms – lopinavir/ritonavir, corticosteroids (including low dose dexamethasone), hydroxychloroquine, azithromycin, tocilizumab and convalescent plasma.

On 16 June 2020, the first results of the RECOVERY study were published on *https://www.recoverytrial.net/*, comparing the efficacy of dexamethasone in COVID-19[21], while the full-text publication appeared in The New England Journal of Medicine on 17 July 2020. The test arm included 2,104 patients, while the control arm (Standard of care, SoC) included 4,321 patients.

The published results of the study, which is the largest clinical trial conducted to date, assessing the safety and efficacy of dexamethasone compared to the standard of care, indicate the need for dexamethasone treatment in the population of patients requiring respiratory support. Publicly available data confirm a clinical benefit in patients requiring invasive mechanical ventilation or oxygen therapy.

The results indicate that in patients hospitalised for COVID-19, the use of dexamethasone is associated with a reduction in 28-day mortality (death rate: 22.9% vs. 25.7%), RR=0.83 (95%CI: 0.75; 0.93), p<0.001. Authors of the study indicate that the risk of death within 28 days was significantly reduced in patients with symptoms persisting for more than 7 days. Analysis by patient subgroups shows that the greatest clinical benefit is obtained in patients undergoing mechanical ventilation (RR = 0.64; 95% CI: [0.51; 0.81]; p<0.001). A statistically significant difference in favour of the dexamethasone arm was also observed in patients requiring oxygen therapy (RR = 0.82; 95% CI: [0.72; 0.94]; p=0.0042). However, no health benefits of dexamethasone were reported in the population of patients not requiring respiratory support (no statistically significant differences).

Patients in the dexamethasone arm had a statistically significantly higher probability of being discharged within 28 days (RR = 1.10; 95% CI: [1.03; 1.17]).

Interpretation of the results should take into account the identified limitations. The uncertainty of the estimates results, among others, from the modification of the study protocol during the clinical trial.

Table 9 contains the description of the methodology and results of the study.

3.1.1.2. Corral 2020

Corral 2020 study is a multi-centre, semi-randomised, non-blinded study. The study included 85 patients – 56 patients were included in the methylprednisolone (MTP) arm (22 were randomised and 34 were assigned based on the doctor's decision), while 29 were included in the arm using SoC without MTP.

The results of Corral 2020 indicate a statistically significant benefit from the use of methylprednisolone in comparison to SoC in terms of the composite outcome – in-hospital death from any cause, deterioration of health resulting in a transfer to the ICU, respiratory failure resulting in the need for implementing invasive ventilation (ITT analysis: (RR=0.55; 95%CI: [0.33; 0.91]; p=0.025)), as well as the transfer to the intensive care unit from the general ward (per-protocol analysis: RR=0.29, 95% CI: [0.1; 0.90]).

The analysis of the death rate and the need for implementing mechanical ventilation indicated no statistically significant differences between the arms of patients who used and who did not use MTP.

Interpretation of the results of Corral 2020 should take into account the identified limitations. The uncertainty of estimates results from the adopted study methodology (partial randomisation, no allocation concealment, no blinding), sample size, differences in the baseline characteristics of patients from the compared arms, as well as the type of publication – pre-print.

Table 10 contains the description of the methodology and results of the study.

3.1.2.Observational studies

3.1.2.1. Methyloprednisolone

Methylprednisolone was used as part of corticosteroid therapy in 5 identified observational studies (Fadel 2020, Wang 2020, Wu 2020a, Sanz Herrero 2020). Sanz Herrero 2020 assessed the efficacy of methylprednisolone as an adjuvant therapy to tocilizumab.

Statistically significant differences in favour of methyloprednisolone versus no GCs/SoC were reported for:

- mortality ratio – Fadel 2020 and Wu 2020a;
- need for mechanical ventilation – Fadel 2020;
- mean hospital stay duration (8 vs. 5 days) – Fadel 2020;
- transfer of the patient to the ICU from the general ward – Fadel 2020;
- composite outcome – transfer to the ICU from the general ward, deterioration of respiratory failure requiring mechanical ventilation, or in-hospital death from any cause – Fadel 2020.

An increase in the risk of transferring a patient to the intensive care unit or death as a result of the use of glucocorticoids was reported in Wang 2020. It should be noted that the results of Wang 2020 should be interpreted taking into account its limitations, primarily in terms of statistically significant heterogeneity in the baseline characteristics of patients from the compared arms, indicating a more severe form of the disease in the arm of patients using methylprednisolone – out of all 55 patients in severe condition, 42 received corticosteroids.

In the study in which methylprednisolone was used as an adjuvant therapy to tocilizumab (Sanz Herrero 2020), a statistically significant reduction in the mortality risk was observed in the glucocorticoid arm compared to patients in the control arm, with statistically significant differences in the extension of hospitalisation time in the MTP arm.

It should be underlined that the above-mentioned primary studies are characterised by a lower reliability level. Due to the methodology used (cohort, retrospective) and the small sample size (<100 patients in Wu 2020a and Sanz Herrero 2020) and significant differences in the baseline characteristics of patients (higher percentage of patients with severe disease in the GCs group – Wang 2020), the results are subject to significant uncertainty.

3.1.2.2. Glucocorticoids

In 10 identified retrospective studies, glucocorticoid therapy was administered with methylprednisolone, dexamethasone, prednisolone, or hydrocortisone in specified, equivalent doses. None of the studies included result analyses of subgroups by the specific GC used.

The results in terms of reducing the mortality risk for comparing the efficacy of glucocorticoids versus SoC in Covid-19 are inconclusive – statistically significant differences in favour of glucocorticoids versus the lack of GCs/SoC were noted in terms of the incidence of in-hospital deaths (Fernandez-Cruz 2020) and reduction of total deaths (Fernandez-Cruz 2020, Bani-Sadr 2020). An increase in the mortality risk in the GCs arm was reported in Wu 2020b and Zhou 2020; in Li 2020, an increase in the mortality risk during hospitalisation in the arm of patients using high doses of GCs was observed.

Statistically significant differences in favour of glucocorticoids versus the lack GCs/ SoC were reported in terms of:

- transfer of the patient to the ICU from the general ward – Albani 2020, Majmundar 2020;
- need for intubation – Majmundar 2020;
- discharge from hospital – Feng 2020, Majmundar 2020.

The results of Wu 2020b, Feng 2020 and Shang 2020 indicate a tendency towards an extension of hospitalisation time in COVID-19 patients treated with glucocorticoids.

Table 5 presents results of primary studies for all analysed outcomes. Additionally, a comparison of the results of the primary studies in terms of mortality rate with the assessment of the significance of the result and the level of reliability of the scientific evidence was carried out. Appendix 1 presents critical evaluations of primary studies which constitute the basis for drawing conclusions on efficacy of corticosteroids in COVID-19.

Table 5. Controlled experimental and observational studies – glucocorticoids. (The results for relative parameters have been taken from the publication)

No.	Study author, year / acronym	Reliability level	Test arm, N	Control arm, N	Death	Transfer to ICU	Need for mechanical ventilation (%)	Hospital discharge	Length of hospitalisation	Disease progression
DEX vs. SoC										
1.	**RECOVERY**	**C**	2,104	4,321	RR=0.83 (95% CI: 0.74; 0.92), NNT=33		RR=0.76 (95% CI: 0.61; 0.96), NNT=52	RR=1.11 (95% CI: 1.04; 1.19), NNT=29		
MTP vs. SoC										
2.	**Corral 2020**	**E**	56	29		ITT: RR=0.52 (95% CI: 0.22; 1.24) PP: RR=0.29 (95% CI: 0.1; 0.90)				
					RR=0.55 (95%CI: 0.33; 0.91), NNT=7					
3.	**Fadel 2020**	**E**	132	81	OR=0.45 (95% CI: 0.22; 0.91), NNT=8	OR=0.47 (95% CI: 0.25; 0.88), NNT=7	OR=0.47 (95% CI: 0.25; 0.92), NNT=7		p <0.001	
4.	**Wang 2020**	**E**	73	42	OR=3.62 (95% CI: 1.26; 10.4), NNT=5					
5.	**Wu 2020a**	**E**	50	34	HR=0.38 (95% CI: 0.20; 0.72), NNT=6					
Glucocorticoids vs. SoC (no GCs)										
1.	**Wu 2020b**	**E**	690	1,073	*HR=1.77 (1.08; 2.89), NNT=7 **HR=2.07 (1.08; 3.98), NNT= 3				*p<0.001	(progression to critical condition) p=0.001
2.	**Fernandez-Cruz 2020**	**E**	396	67	HR=0.51 (95% CI: 0.27; 0.96), NNT=10					
3.	**Albani 2020**	**E**	559	844		OR=0.48 (95% CI: 0.34; 0.66), NNT=18				
4.	**Bani-Sadr 2020**	**E**	119	85	HR=0.47 (95% CI: 0.23; 0.97), NNT=50					
5.	**Feng 2020**	**E**	75	331					p<0.001	##
6.	**Shang 2020**	**E**	*76, **77	*150, **62					p<0.05	
7.	**Lu 2020**	**E**	151	93						
8.	**Majmundar 2020**	**E**	60	145		HR=0.15 (95% CI: 0.07; 0.33)	Intubation: HR=0.31 (95% CI: 0.14; 0.70)	HR=0.16 (95% CI: 0.07; 0.34)		
9.	**Li 2020**	**E**	341	207	#High doses: HR=3.5 (95% CI: 1.8; 6.9) #Low doses:					
10.	**Zhou 2020**	E	57	134	$OR=2.79 (95%CI: 1.44; 5.38)					
MTP + TOC + SoC vs. TOC + SoC (no GCs)										
1.	**Sanz Herrero 2020**	**E**	56	16	RR=0.20 (95% CI: 0.08; 0.47), NNT=2				p=0.028	

* severe condition; ** critical condition; # death during hospitalisation; ## disease progression as the need for mechanical ventilation or death; $ AOTMiT's own calculations

3.1.3. Efficacy analysis for mortality risk

Table 6. Summary of data on mortality – glucocorticoids

Study	Test arm, n/N (%)	Control arm, n/N (%)	Result, relative parameter (95% CI)	Reliability level
Dexamethasone vs. SoC				
RECOVERY	[1]482/2 104 (22.9%) [2]95/324 (29.3%) [3]298/1,279 (23.3%) [4]89/501 (17.8%)	[1]1110/4321 (25.7%) [2] 283/683 (41.4%) [3] 682/2,604 (26.2%) [4] 145/1,034 (14%)	[1]RR=0.83 (0.75; 0.93); NNT=33 [2]RR=0.64 (0.51; 0.81), NNT=9 [3]RR=0.82 (0.72; 0.94), NNT=30 [4]RR=1.19 (0.91; 1.55)	C
Methylprednisolone vs. SoC				
Corral 2020	12/56 (21%)[#] 9/49 (18%)[##]	5/29 (17%)	RR=1.24 (0.49; 3.19)[#] RR=1.07 (0.40; 2.87)[##]	E
Fadel 2020	18/132 (13.6%)	21/81 (26.3%)	OR=0.45 (0.22; 0.91), NNT=8	E
Wang 2020[&]	24/73 (32.9%)	5/42 (11.9%)	OR=3.62 (1.26; 10.4), NNT=5	E
Wu 2020a	23/50 (46.0%)	21/34 (61.8%)	HR=0.38 (0.20; 0.72) $OR=0.53 (0.12; 1.28)	E
Glucocorticoids vs. SoC				
Wu 2020b	*83/531 (15.6%) **70/159 (44.0%)	*26/983 (2.6%) **14/90 (15.6%)	$OR=6.8 (4.33; 10.74), NNT=7 $OR=4.2 (2.23; 8.18), NNT=3	E
Fernandez-Cruz 2020	55/396 (13.9%)	16/67 (23.9%)	HR=0.51 (0.27; 0.96) $OR=0.51 (0.27; 0.97), NNT=10	E
Albani 2020	171/559 (30.6%)	183/844 (21.7%)	OR=1.57 (1.23; 2.01) $OR=1.59 (1.25; 2.03), NNT=11 ^OR=1.15 (0.90; 1.45)	E
Bani-Sadr 2020	31/172 (18%)	17/85 (20%)	HR=0.47 (0.23; 0.97) $OR=0.88 (0.46; 1.70)	E
Feng 2020	21/52 (40.4%)	8/18 (44.4%)	$OR=0.85 (0.29; 2.50)	E
Zhou 2020	26/57 (45.6%)	31/134 (23.1%)	$OR=2.79 (1.44; 5.38), NNT=4	E
Lu 2020	NDA	NDA	OR=1.05 (0.15; 7.46)	E
Majmundar 2020	8/NDA (14.55%)	34/NDA (25%)	^^HR=0.53; (0.22; 1.31) ^^^HR=0.62 (0.29; 1.35)	E
Li 2020	NDA	NDA	High doses of GCs: ^^HR=3.5 (1.8; 6.9) ^^^HR=3.32 (1.85; 5.97) Low doses of GCs:^^HR=1.26 (0.61; 2.58)^^^HR=1.07 (0.57; 2.01)	E
MTP + TOC + SoC vs. TOC + SoC (no GCs)				
Sanz Herrero 2020	11/56 (19.6%)	10/16 (62.5%)	RR=0.20 (95% CI: 0.08; 0.47) $OR=0.15 (0.04; 0.49), NNT=2	E

1 – Patients (total); 2 – Patients requiring ventilation (at baseline); 3 – Patients requiring oxygen therapy; 4 – Patients not requiring breathing support; [&]Compound outcome – admission to the ICU or death # ITT ## *per protocol*; *severe condition; ** critical condition; ^analysis taking confounders into account; ^^adjusted result; ^^^non-adjusted result; $ AOTMiT's own calculations

Figure 1. Results of experimental prospective studies (RECOVERY, Corral 2020) expressed as relative risk (RR) of death for the GCs vs. SoC comparison/ not using GCs

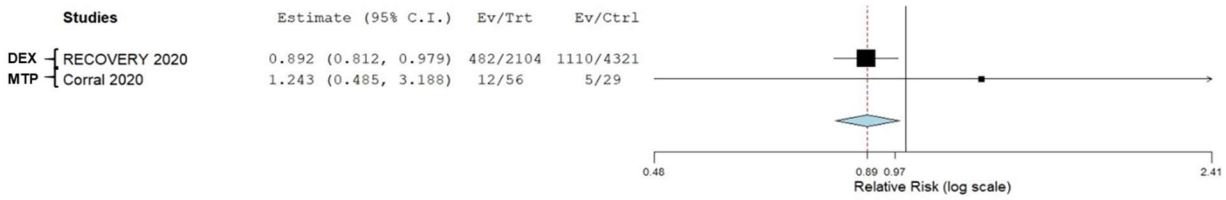
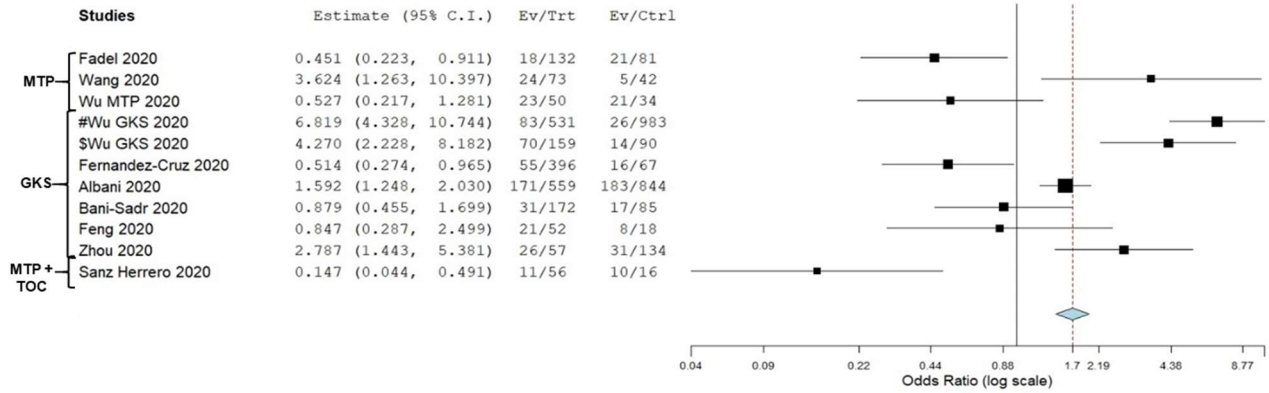


Figure 2. Results of observational retrospective studies (RECOVERY, Corral 2020) expressed as odds ratio (OR) of death for the GCs vs. SoC comparison/not using GCs



– patients in severe condition; $ – patients in critical condition

3.2. Results of secondary studies

Table 8 presents a description of methodology and conclusions drawn based on the identified secondary studies.

The identified secondary studies (Gangopadhyay 2020, Lu 2020, Ye 2020, Singh 2020) constitute an analysis of results of studies characterised by lower quality (observational studies – mainly cohort or retrospective studies). Only the systematic review Singh 2020 included a randomised controlled trial (RECOVERY).

It should be underlined that not all primary studies included in the identified systematic reviews meet inclusion criteria to the systematic review conducted by the AOTMiT. A summary of primary studies included in the AOTMiT's review and identified secondary studies is presented in Table 7.

Results of Gangopadhyay 2020 suggest lack of statistically significant differences with regard to mortality risk in critical COVID-19 patients in whom corticosteroids were used, compared to patients not subjected to treatment. **Authors of the paper state that corticosteroids should be used in patients with COVID-19 and critical illness-related corticosteroid insufficiency (CIRCI).** The use of corticosteroids should also be considered in patients with acute respiratory distress syndrome (ARDS).

Authors of Lu 2020, a systematic review and meta-analysis, state that **corticosteroid therapy can increase the mortality risk in patients with mild COVID-19.** No association between corticosteroid therapy and mortality in severely symptomatic patients was found. In the context of clinical trials, a short-term systemic glucocorticoid therapy may be acceptable.

Authors of the Ye 2020 systematic review have concluded that the use of corticosteroids can reduce the mortality risk and shorten the need for mechanical ventilation in COVID-19 patients with ARDS (low-quality evidence). In patients with severe (but not critical) COVID-19, the results of the meta-analysis of two studies did not reach statistical significance, however, the authors of the review indicate that the use of glucocorticoids may increase the mortality risk (very low-quality evidence).

The Singh 2020 systematic review indicated that it is difficult to draw firm conclusions about the therapeutic benefits of corticosteroids based on the available observational studies. **However, attention should be paid to RECOVERY, a study in which the use of dexamethasone in severe patients allowed for obtaining significantly better results than in the control arm.** At the same time, authors of the paper indicated that, for drawing clear conclusions on the effectiveness of corticosteroids in COVID-19 treatment to be possible, confirmation of the RECOVERY results in subsequent, methodologically correct clinical trials is crucial.

Table 7. A summary of trials included in to the AOTMiT's review and secondary studies included in the analysis.

Study	AOTMiT	Gangopadhyay 2020	Lu 2020	Ye 2020	Singh 2020
Horby 2020 (RECOVERY)	+	-	-	-	+
Corral 2020	+	-	-	-	-
Fadel 2020	+	-	-	-	+
Wang 2020	+	+	-	+	+
Wu 2020a	+	+	+	+	+
Wu 2020b	+	-	-	-	-
Fernandez-Cruz 2020	+	-	-	-	-
Albani 2020	+	-	-	-	-
Bani-Sadr 2020	+	-	-	-	-
Feng 2020	+	-	-	-	-
Shang 2020	+	-	+	-	-
Zhou 2020	+	+	+	-	-
Lu 2020	+	+	-	+	+

Study	AOTMiT	Gangopadhyay 2020	Lu 2020	Ye 2020	Singh 2020
Majmundar 2020	+	-	-	-	-
Li 2020	+	-	-	+	-
Sanz Herrero 2020	+	-	-	-	-
Choroboczek 2020	-^	-	-	-	+
Guan 2020	-^	+		-	-
Xu 2020	-^^	-	-	+	-
Yan 2020	-^^	-	-	+	-
Yin 2020	-^	-	+	-	-
Ni 2020	-^	-	+	-	-

„+" study included in the review; „-" study not included in the review; ^ - not sufficiently big sample; ^^ lack of analysis of outcomes for the efficacy or safety profile of GCs

Table 8. Characteristics of secondary studies included in the review

Study	Methodology	Number/methodology of included primary studies	AMSTAR II quality score	Results	Conclusions
Gangopadhyay 2020 PRE-PRINT paper	Meta-analysis – use of corticosteroids in treatment of critical COVID-19 patients. **Inclusion criteria:** • separate results for patients treated with and untreated with corticosteroids; • coronavirus infection study; • acute respiratory distress syndrome (ARDS) had to occur as a result of the coronavirus infection; • all patients in the active therapy arm had to be treated with steroids. The abstract indicates that the studies were selected based on the PICO criteria, but the publication did not present them. The study did not take into account review publications, single case studies and publications in which separate results for patients treated with steroids were not presented. Cochrane Collaboration was used to evaluate the included studies. The risk of systemic bias was assessed using the "*funnel plots*" method.	Only results regarding COVID-19 were analysed and described in this paper. Nine studies meeting the inclusion criteria were found and included in the review. Out of these, 5 studies concerned COVID-19 patients (cohort studies, N = 1781): – Wu 2020 (N=201, GCs - 84, no-GCs - 117), – Zhou 2020 (N=191, GCs – 59, no-GCs - 132), – Guan 2020 (N=1099, GCs – 37, no-GCs - 1062), – Wang 2020 (N=46, GCs no-GCs - 46), – Lu 2020 (N=244, GCs – 87, no-GCs – 157).	**Moderate quality**	No statistically significant difference in mortality between patients treated and not treated with corticosteroids was observed: • RR=1.26 (95CI: 0.95-1.66) p=0.095; I^2 = 74.46); Wu 2020, Wan 2020 and Lu 2020 are studies which took only ARDS patients into account. The meta-analysis of these studies also indicated no statistically significant differences in mortality between patients treated and not treated with corticosteroids: • RR=0.91 (95%CI: 0.63-1.325) p=0.636; I^2=63.38);	Corticosteroids should be used in patients with COVID-19 and critical illness-related corticosteroid insufficiency (CIRCI), their use can be considered in patients with ARDS. The results of the meta-analysis did not reveal a higher mortality in critically ill COVID-19 patients treated with corticosteroids versus those not treated with corticosteroids. Despite numerous limitations, mainly related to the methodology of the included studies (retrospective studies), the meta-analysis indicates the harmlessness of the use of corticosteroids in critically ill patients with COVID-19 and ARDS.
Lu 2020	Systematic review with a meta-analysis **Inclusion criteria:** **P**: patients diagnosed with COVID-19, SARS or MERS **I**: corticosteroids, corticosteroids + systemic therapy **C**: placebo, systemic therapy **O**: mortality (primary outcome), duration of pneumonia, duration of hospitalisation, duration of fever, other adverse events such as: infections (bacterial or fungal), kaliopenia, osteonecrosis of femoral head (ONFH). **S**: Randomised clinical trials (RCTs), cohort-controlled studies comparing corticosteroids to	Only results regarding COVID-19 were analysed and described in this paper. 23 studies which met the inclusion criteria were included in the review. Of them, 5 (cohort) studies regarded COVID-19 patients: – Zhou 2020 (adults, all severity forms of disease), N=191, intervention: corticosteroids), – Wu 2020 (adults, severe form of the disease, N=201,	**High quality**	Mortality was assessed in 4 studies (N=737). Glucocorticoid therapy did not reduce the risk of death in COVID-19 patients (RR=2.0; 95% CI: 0.7; 5.8; I^2=90.9%). Fever duration was assessed in 1 study. Fever duration in COVID-19 patients was statistically significantly shorter in the arm receiving corticosteroids than in the control arm (WMD=-3.2 days; 95% CI: -3.6; -2.9). Pneumonia duration was assessed in 1 study. No statistically significant differences regarding duration of pneumonia between the arm receiving corticosteroids and the control arm were observed (WMD=-1.0 days; 95% CI: -2.9; 0.9).	Corticosteroid therapy may increase the risk of death in coronavirus patients with mild symptoms of the disease. No association between corticosteroid therapy and mortality in severely symptomatic patients was found. In the context of clinical trials, a short-term systemic corticosteroid therapy may be acceptable.

Study	Methodology	Number/methodology of included primary studies	AMSTAR II quality score	Results	Conclusions
	placebo, or combination of corticosteroids and systemic therapy with systemic therapy alone. Only full-text publications in English or Chinese were included. Conference abstracts and studies in which necessary information had been omitted were not included in the review. The included studies were assessed with the use of: Cochrane risk-of-bias tool for RCTs, and the NOS scale for cohort studies. The quality of evidence was assessed using GRADE.	intervention: methylprednisolone), – Yin 2020 (adults, severe form of the disease, N=46, intervention: methylprednisolone), – Shang 2020 (adults, moderate or severe form of the disease, N=416, intervention: methylprednisolone), – Ni 2020 (adults, moderate or severe form of the disease, N=72, intervention: methylprednisolone).		Hospitalisation duration was assessed in 1 study. Patients receiving corticosteroids required a longer hospitalisation than patients not receiving such treatment (WMD=2.4; 95% CI: 1.4; 3.4). A meta-analysis of results on the safety of use of corticosteroids in COVID-19 was not carried out. **Assessment and limitation of the included studies according to authors of the review:** The quality of evidence was very low. GRADE scores for all endpoints (mortality, duration of fever, duration of pneumonia, duration of hospitalisation) were very low. The NOS score of the studies was as follows: Zhou 2020: 4 points, Wu 2020: 5 points, Yin 2020: 5 points, Shang 2020: 5 points, Ni 2020: 5 points Due to the limited number of studies, it was not possible to perform subgroup analyses by dose and type of the administered corticosteroids.	
Ye 2020	Systematic review with a meta-analysis **Inclusion criteria:** • randomised clinical trial (RCT), cohort and clinical-cohort studies comparing the use of corticosteroids vs. lack of corticosteroids in patients with COVID-19, SARS or MERS. The included studies were assessed with the use of: Cochrane risk-of-bias tool for RCTs, and the NOS scale for observational studies. ROBIS risk of bias tool for systematic reviews. The quality of evidence was assessed using GRADE.	Only results regarding COVID-19 were analysed and described in this paper. Of the studies included in the study, 6 were conducted on the COVID-19 patient population and all were cohort studies: – Wu 2020 for the population of COVID-19 patients with ARDS (n=84) – Li 2020, Lu 2020, Wang 2020, Xu 2020 and Yan 2020 for the population of COVID-19 patients without ARDS (N=679).	**Moderate quality**	COVID-19 patients with ARDS (n=84): • in Wu 2020 – statistically significant mortality reduction (HR=0.41, 95% CI: 0.20; 0.83, MD 29.2%) – low quality of evidence. Population of patients with severe (not critical) COVID-19 – in patients using corticosteroids: • meta-analysis of Li 2020 and Lu 2020 (n=331) – possible increase of mortality, however differences were not statistically significant (HR=2.30 (95% CI: 1.00; 5.29); • Wang 2020 reports an increase of risk with regard to the compound endpoint: death or admission to the ICU • Xu 2020 and Yan 2020 suggest a longer viral clearance time. Very low quality of evidence.	Corticosteroid therapy may reduce the risk of death and shorten the time needed for mechanical ventilation in COVID-19 patients with ARDS (low-quality evidence) and may also increase the risk of death in patients with severe, but not critical, COVID-19 (very low-quality evidence).

Study	Methodology	Number/methodology of included primary studies	AMSTAR II quality score	Results	Conclusions
Singh 2020	Systematic review on the role of corticosteroids in COVID-19. **Inclusion criteria:** No access to the appendix in which the description was included. No information on the tools used to assess the included studies.	Only results regarding COVID-19 were analysed and described in this paper. 6 studies assessing the therapeutic effect of corticosteroids, including: – 1 RCT (RECOVERY Trial)4; – 1 prospective quasi-experimental study (Fadel 2020); – retrospective study (Wu 2020, Lu 2020, Wang 2020, Choroboczek 2020).	**Low quality / critically low quality***	*RECOVERY – results were described in chapter 4.1.1. of the document.* Of the 5 observational studies (4 retrospective and 1 quasi-prospective studies), 3 demonstrated a benefit of using corticosteroids and 2 failed to demonstrate any benefit. Improvements in parameters of severely ill and critically ill COVID-19 patients using corticosteroids have been observed in the following areas: Reduction of hospitalization time, prevention of deterioration of respiratory parameters, progression to ARDS (Fadel 2020), faster return of temperature and oxygenation to regular levels (Wang 2020), reduction of the frequency of intubation and mechanical ventilation (Choroboczek 2020). None of the above-listed studies evaluated the treatment of patients with mild COVID-19, and the majority of patients were administered other drugs as well.	The results of observational studies are heterogeneous, which hinders drawing firm conclusions on the therapeutic benefits of corticosteroids. However, attention should be paid to RECOVERY, a study which demonstrated much better results in sever patients in whom dexamethasone was administered. At the same time, it should be pointed out that more studies which would replicate the result obtained in RECOVERY are required to draw relevant conclusions.

*Lack of access to materials indicated in the content of the review as supplementary information on the adopted methodology.

Abbreviations: N – number of patients in the study / arm; RR – relative risk; CI – confidence interval; I^2 – research heterogeneity index; WMD – weighted mean differences); NOS – Newcastle-Ottawa Scale; GRADE – Grading of Recommendation Assessment, Development and Evaluation; GCs – glucocorticoids; no-GCs – no glucocorticoids

4. CONCLUSIONS

The conducted review of scientific evidence identified 1 randomised clinical trial allowing for drawing conclusions about the possible positive therapeutic effect of the use of glucocorticoids in the form of dexamethasone in COVID-19 patients. At the same time, it should be noted that the aforementioned benefits are noticeable only in the population of severe COVID-19 patients, i.e. requiring mechanical ventilation or oxygen therapy.

The results of the identified primary studies in which methylprednisolone was added to standard therapy indicate possible benefits over patients treated without MTP in terms of reducing mortality and the frequency of transferring patients to the intensive care unit.

An analysis of the results of the identified observational studies, presenting the results for GCs without specifying particular drugs, does not allow for drawing unequivocal conclusions regarding the influence of glucocorticoids on the obtained therapeutic effects compared to standard of care without GCs. However, it should be pointed out that the statistically significantly longer hospitalisation time observed in 4 studies in patients using glucocorticoids may be related to the tendency towards more frequent use of glucocorticoids in patients with more severe COVID-19 – no data are available to compare the baseline patient characteristics of patients in the test and control.

The identified primary studies are characterised by numerous limitations (the retrospective nature of most studies, short observation time, heterogeneity in terms of the baseline characteristics of patients, low sample size, lack of subgroup analyses broken down by specific GCs), and their reliability is assessed as low.

The results of the identified secondary studies are consistent with the conclusions of the conducted review. Therefore, the need for conducting further studies characterised by higher quality is underlined.

APPENDIX

Table 9. Description of the methodology and results of RECOVERY (Horby 2020)

<table>
<tr><th colspan="7">RECOVERY Trial (Randomised Evaluation of COVid-19 thERapY), NCT04381936</th></tr>
<tr><th colspan="7">Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report</th></tr>
<tr><th>Methodology</th><th colspan="2">Population</th><th>Intervention</th><th>Control</th><th>Standard clinical practice</th><th>Limitations</th></tr>
<tr><td rowspan="2">RCT, open-label, multicentre, phase II, III;

Randomisation 1:2</td><td colspan="2" rowspan="2">N=6425,
Inclusion criteria: hospitalisation; SARS-CoV-2 infection (clinically suspected or laboratory confirmed); no medical history that might, in the opinion of the attending clinician, put patients at substantial risk if they were to participate in the trial. Initially, recruitment was limited to patients who were at least 18 years of age, but the age limit was removed starting on 9 May 2020. Pregnant or breastfeeding women were eligible.</td><td>Ni=2104
Glucocorticoids – dexamethasone (6 mg once daily i.v. or p.o. / 10 days)
n= 2 104 (one of the study arms*)</td><td>Nc=4,321
Standard therapy</td><td rowspan="15">There is no established COVID-19 procedure in Poland</td><td rowspan="15">– Protocol modifications during the course of the study;
– Randomisation without stratification;
– 12% of patients in the DEX arm and 10% of patients in the control arm with a negative SARS-CoV-2 test result;
– No information about loss of patients from the study;
– In the control arm, 8% of patients received dexamethasone as part of clinical care;
– The publication includes preliminary research results.</td></tr>
<tr><td colspan="2">In both arms: lopinavir / ritonavir (0.5% vs. 0.5%), hydroxychloroquine (1% vs. 1%), azithromycin (24% vs. 25%), tocilizumab or sarilumab (2% vs. 3%) were administered</td></tr>
<tr><th colspan="5">Baseline population characteristics</th></tr>
<tr><td colspan="3">Age, mean – years (SD)</td><td>66.9 (15.4)</td><td>65.8 (15.8)</td></tr>
<tr><td colspan="3"><70</td><td>54%</td><td>58%</td></tr>
<tr><td colspan="3">≥70 to <80</td><td>22%</td><td>20%</td></tr>
<tr><td colspan="3">≥80</td><td>24%</td><td>22%</td></tr>
<tr><td colspan="3">Men, n (%):</td><td>1,338 (64)</td><td>2,750 (64)</td></tr>
<tr><td rowspan="3">Respiratory support received, n (%)</td><td colspan="2">No oxygen therapy</td><td>501 (24)</td><td>1,034 (24)</td></tr>
<tr><td colspan="2">Oxygen therapy</td><td>1,279 (61)</td><td>2,604 (60)</td></tr>
<tr><td colspan="2">Invasive mechanical ventilation</td><td>324 (15)</td><td>683 (16)</td></tr>
<tr><td rowspan="8">Previous coexisting disease (%)</td><td colspan="2">Diabetes</td><td>25</td><td>24</td></tr>
<tr><td colspan="2">Heart disease</td><td>28</td><td>27</td></tr>
<tr><td colspan="2">Chronic lung disease</td><td>20</td><td>22</td></tr>
<tr><td colspan="2">Tuberculosis</td><td><0.5</td><td><0.5</td></tr>
<tr><td colspan="2">HIV</td><td>1</td><td><0.5</td></tr>
<tr><td colspan="2">Severe liver disease</td><td>2</td><td>2</td></tr>
<tr><td colspan="2">Severe kidney impairment</td><td>8</td><td>8</td></tr>
<tr><td colspan="2">Any</td><td>56</td><td>56</td></tr>
</table>

RECOVERY Trial (Randomised Evaluation of COVid-19 thERapY), NCT04381936							
Results							
Outcome		**Therapy duration (days)**	**Intervention – dexamethasone**	**Control – SoC**	**Relative parameter RR (95% CI)^^**	**NNT (95% CI)**	**Clinical relevance**
28-day mortality rate, n/N (%)	Total	Median time for DEX: 6 days	482/2104 (22.9)	1110/4321 (25.7)	**0.83 (0.75;0.93)**	**33 (19.1;112.1)^**	
	Patients requiring ventilation (at baseline)		95/324 (29.3)	283/683 (41.4)	**0.64 (0.51;0.81)**	**8^^ 9 (5.6;18.1)^**	
	Patients requiring oxygen therapy		298/1,279 (23.3)	682/2604 (26.2)	**0.82 (0.72;0.94)**	**25^^ 30 (16.2;175.6)^**	
	Patients not requiring respiratory support		89/501 (17.8)	145/1,034 (14)	1.19 (0.91;1.55)	-	
Duration of hospitalisation			12 days	13 days	-	-	
Discharged from hospital within 28 days (%)			1,413 (67.2)	2,745 (63.5)	**1.10 (1.03;1.17)**	**29 (16.5;94.6)^**	
Need for invasive mechanical ventilation or death, n/N (%)**			456/1780 (25.6)	994/ 3638 (27.3)	0.92 (0.84;1.01)	-	
Invasive mechanical ventilation			102/1,780 (5.7)	285/3638 (7.8)	**0.77 (0.62;0.95)**	**52 (30.8;166.9)^**	
Death, n/N (%)			387/1,780 (21.7)	827/3,638 (22.7)	0.92 (0.84;1.03)	-	
Conclusions: Researchers indicate that dexamethasone therapy reduces mortality by 30% in patients undergoing mechanical ventilation and by 20% in patients receiving oxygen therapy. Importantly, the drug has not been shown to be effective in patients who do not require respiration support.							

*Other glucocorticoids: prednisolone (max: 40 mg) - pregnant or breastfeeding women; methylprednisolone (max: 32 mg); hydrocortisone as additional option at prematures (0,5 mg/kg every 12 h for 7 days, every 3 days later); Interventions in other study arms: Lopinavir/Ritonavir (400mg, 100mg every 12 h /10 days); Hydroxychloroquine (for 10 days); Azithromycin (500mg /d for 10 days); Single unit of ABO compatible convalescent plasma (275mls +/- 75 mls) intravenous per day on study days 1 (as soon as possible after randomisation) and 2 (with a minimum of 12 hour interval between 1st and 2nd units); Tocilizumab (dose depend on body weight); ** in patients not requiring mechanical ventilation at baseline; ^ AOTMiT's own calculations; ^^ publication data

Table 10. Description of the methodology and results of Corral 2020

Corral 2020					
GLUCOCOVID: A controlled trial of methylprednisolone in adults hospitalized with COVID-19 pneumonia					
Methodology	**Population**	**Intervention**	**Control**	**Standard clinical practice**	**Limitations**
Controlled clinical trial, partially randomised, open-label, multicentre Duration of the study: April-May 2020 (no details)	N=85 Patients with a laboratory confirmed diagnosis of SARS-CoV-2 infection Inclusion criteria: age ≥ 18 years; symptom duration of at least 7 days; Radiological evidence of lung disease in chest X-ray or CT-scan; Moderate-to-severe disease with abnormal gas exchange: PaFi (PaO2/FiO2) < 300, or SAFI (SAO2/FiO2) < 400, or at least 2 criteria of the BRESCIA-COVID Respiratory Severity Scale (BCRSS); Laboratory parameters suggesting a hyper-inflammatory state: serum C-Reactive Protein (CRP) >15 mg/dL, D-dimer > 800 mg/dl, ferritin > 1000 mg/dL or IL-6 levels > 20 pg/ml. Exclusion criteria: Patients were excluded if they were intubated or mechanically ventilated, were hospitalized in the ICU, were treated with corticosteroids or immunosuppressive drugs at the time of enrolment, have chronic kidney disease on dialysis, were pregnant or refused to participate.	Ni=56 (of which: non-randomised arm[#] - 22; randomised arm-34) Methyloprednisolone 40mg i.v. every 12h / 3 days followed by 20 mg every 12h /3 days + SoC	Nc=29 SoC	There is no established COVID-19 procedure in Poland	– Partial randomisation of the study (some patients were randomised to the intervention arm; others were assigned based on the physician's preference); – Significant differences between groups in patient characteristics: SaO2/FiO2 (p<0.001) or CRP (p=0.016); – Small sample size; – Result from interim analysis; – Lack of information about the dosages of other therapies and follow up; – Potential differences in treatment schemes between medical centres; – Due to the rapidly deteriorating course of some COVID-19 cases, they escalated to ICU or NIV within the first 24 hours of inclusion in the study; – Pre-print status.
	Age in years, average (SD)[##]	67 (11)	72 (13)		
	SaO_2/FiO_2, average (SD)[##]	327 (93)	218 (86)		
	CRP, average (SD) [##]	14.3 (8.3)	18.8 (8.0)		

Results							
Outcome		**Observation time**	**Intervention**	**Control**	**RR (95% CI)^^**	**NNT (95% CI)**	**Clinical relevance**
Compound outcome – ICU admission, need for invasive ventilation or death**	ITT analysis	NDA	19/56 (34%)	14/29 (48%)	**0.55 (0.33; 0.91) / p=0.025**	**7***	
	per-protocol analysis		12/49 (24%)	14/29 (48%)	**0.37 (0.19; 0.74) / p=0.0037**	**5 (2.2; 50.6)***	
Death			12/56 (21%)[#] 9/49 (18%)[##]	5/29 (17%)	1.24 (0.49; 3.19)*[#] 1.07 (0.40; 2.87)*[##]	-	
ICU admission			8/56 (14%)[#] 4/49 (8%)[##]	8/29 (28%)	0.52(0.22; 1.24)*[#] **0.29 (0.1; 0.90)***[##]	-	
Need for invasive ventilation			6/56 (11%)[#] 3/49 (6%)[##]	3/29 (10%)	1.04 (0.28; 3.84)*[#] 0.79 (0.19; 3.28)*[##]	-	
The use of methylprednisolone was associated with a reduced risk of the occurrence of the composite outcome in the age-stratified ITT analysis (RR = 0.55 [95% CI: 0.33, 0.91]; p = 0.024). In the per protocol analysis, the RR was 0.11 (0.01, 0.83) in patients aged ≤ 72 years, 0.61 (0.32, 1.17) in the> 72 years group and 0.37 (0, 19-0.74, p = 0.0037) in the entire group after stratification by age. The decrease in C-reactive protein levels was more pronounced in the methylprednisolone group (p = 0.0003).							
The authors' conclusions suggest that the use of a short course of methylprednisolone treatment may have a beneficial effect on the clinical outcome of severe COVID-19 pneumonia, reducing the risk of admission to the intensive care unit, mechanical ventilation or death.							

* AOTMiT's own calculations; ** age-stratified analyses; *** publication data; ^ if the clinical team decided that a strong preference for glucocorticoid therapy existed; # ITT analysis; ## ¬per protocol analysis

Table 11. Description of the methodology and results of Fadel 2020

Fadel 2020						
Early Short Course Corticosteroids in Hospitalized Patients with COVID-19						
Methodology	**Population**		**Intervention**	**Control**	**Standard clinical practice**	**Limitations**
Observational, quasi-experimental, multicentre study conducted in 5 hospitals in Michigan Duration of the study: 12 - 27/03/2020	N=213 patients Patients with confirmed moderate to severe COVID-19 Inclusion criteria: age ≥18 years, confirmed COVID-19 infection, with radiographic evidence of bilateral pulmonary infiltrates, and required oxygen by nasal cannula, high-flow nasal cannula (HFNC), or mechanical ventilation. Exclusion criteria: patients transferred from an out-of-system hospital, died within 24 hours of presentation to the ED, or were admitted for less than 24 hours.		Ni=132 methylprednisolone 0.5 - 1 mg / kg / day divided in 2 i.v. doses for 3 days + SoC	Nc=81 SoC (oxygen therapy, HFNC, invasive ventilation, antibiotic agents, antiviral agents, vasopressor support, and renal-replacement therapy)	There is no established COVID-19 procedure in Poland	– There are differences in the baseline patient characteristics of the compared arms: – Short observation period; – Incomplete reporting of results of the analysis; – The exact observation time for the study was not reported; – Some patients in the control arm were taking glucocorticoids after the updated COVID-19 treatment protocol was implemented; – By 9 April 9 2020, 51 (62.9%) patients in the SoC cohort and 88 (66.7%) patients in the early corticosteroid cohort had been discharged from the hospital; the results in these patients are unknown.
	Age (IQR)		61 (51-72)	64 (51.5-3.5)		
	Men		68 (51.5)	41 (50.6)		
	Coexisting conditions (%)	Asthma	12.9	19.8		
		Chronic kidney disease	43.5	51.9		
		COPD	9.1	18.5		
		Diabetes	51.5	45.7		
		Hypertension	72.7	76.5		
		Coronary disease	15.2	22.2		
	Other therapies (%)	Antibiotics	74	80.2		
		Hydroxychloroquine	78.8	70.4		
		Lopinavir/ritonavir	0.76	11.1		
		Remdesivir	0	6.2		
		Tocilizumab	4.5	10.1		
		GCs (received at any time)	68.2	56.8		
		GCs (received within 48h)	41.7	12.4		
	Median time to steroid initiation from admission (IQR)		2 (1-3)	5 (3-7)		
	Methylprednisolone use (%)		95.5	93.5		

Results						
Outcome	**Observation time**	**Intervention**	**Control**	**Relative parameter / p**	**NNT**	**Clinical relevance**
Median hospital length of stay	min. 14 days	5 days	8 days	p <0.001	NDA	
Primary composite outcome - escalation from GMU to ICU, respiratory failure requiring mechanical ventilation, death		46/132 (34.9%)	44/81 (54.3%)	**OR=0.45 (0.26; 0.79)**	**5 (3;17)^**	

Fadel 2020						
Deaths		18/132 (13.6%)	21/81 (26.3%)	**OR=0.45 (0.22; 0.91)**	**8 (5;92)^**	
Respiratory failure requiring mechanical ventilation*		26/120 (21.7%)	26/71 (36.3%)	**OR=0.47 (0.25; 0.92)**	**7 (4;65)^**	
Escalation from GMU to ICU **		32/117 (27.3%)	31/70 (44.3%)	**OR=0.47 (0.25; 0.88)**	**7 (4;37)^**	
Early short course of methylprednisolone in moderate to severe COVID-19 patients may improve the clinical outcomes and reduce duration of hospitalisation.						

* A total of 10 and 12 patients were not included in this analysis because they required mechanical ventilation in the emergency department in the SOC and early corticosteroid group, respectively.; ** A total of 11 and 15 patients were not included in this analysis because they were directly admitted to the intensive care unit in the SOC and early corticosteroid group, respectively; ^ AOTMiT's own calculations

Table 12. Description of the methodology and results of Wang 2020

Wang 2020					
No Clear Benefit to the Use of Corticosteroid as Treatment in Adult Patients with Coronavirus Disease 2019: A Retrospective Cohort Study					
Methodology	**Population**	**Intervention**	**Control**	**Standard clinical practice**	**Limitations**
Retrospective, single-centre, cohort study Duration of the study: 18/01/2020–28/02/2020	N=115 (including 55 in critical condition) Patients with laboratory-confirmed COVID-19; Number of severe cases (%): 55/115 (48%), of which 42 patients received corticosteroids. All patients were treated with moxifloxacin (0.4 g/day), umifenovir (0.2 g every 8 hs.) and ribavirin (0.5 g every 12 hs). Inclusion criteria: - patients with rRT-PCR-confirmed SARS-CoV-2 infection aged ≥ 18 years old	Ni=73 I.v. methylprednisolone 0.5 - 1 g day for 2-3 days or 1 - 3 mg/kg of body weight/day for 3-10 days	Nc=42 other treatments that do not include glucocorticoids Other treatments include: immunoglobulins, interferon-α, traditional Chinese medicine (as monotherapy or any combination)	There is no established COVID-19 procedure in Poland	– Small sample size; – The dosage of other therapies was not reported; – Patient observation time was not reported; – There was no stratification, e.g. by dose of GCs; – There were statistically significant differences in the baseline patient characteristics between the compared arms – the corticosteroid arm included a higher percentage of severe patients; – There were significant discrepancies in the number of patients with at least 1 co-morbid disease in the publication - the total indicated number of patients does not equal the number of patients given by group; – Pre-print status.
	Age (IQR)	61 (42-68)	51 (34-65)		
	Men (%)	50.7	50		
	Number of patients with at least 1 comorbidity[2]:	34/73 (46.6%)	11/42 (26.2%)		

Results						
Outcome	**Observation time**	**Intervention**	**Control**	**Relative OR parameter (95% CI)**	**NNT**	**Clinical relevance**
Transfer of the patient to the ICU or death [n/N], (%)	NDA	24/73 (32.9%)	5/42. (11.9%)	**OR=3.62 (1.26; 10.4)**	**5 (3; 16)***	
The authors of the study concluded that there is no evidence of any benefit of glucocorticoid use in adult COVID-19 patients.						

* Agency's own calculations

[2] The publication included discrepancies in the number of patients with at least 1 co-morbid disease – see limitations.

Table 13. Description of the methodology and results of Wu 2020a

Wu 2020a					
Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan					
Methodology	**Population**	**Intervention**	**Control**	**Standard clinical practice**	**Limitations**
Retrospective, single-centre cohort study Duration of the study: Patients admitted between 25/12/2019 and 26/01/2020; Observation until 13/02/2020	COVID-19 patients, ARDS subpopulation: N=84 patients Age, median (IQR), years: 58.5 (50-69) Men:60 (71.4%)	Ni=50 patients with ARDS Methylprednisolone + SoC (i.a. antiviral drugs, antibiotics, interferon-alpha)	Nc=34 patients with ARDS Methylprednisolone not used SoC (i.a. antiviral drugs, antibiotics, interferon-alpha)	There is no established COVID-19 procedure in Poland	– No detailed information on the treatment used; the dosage of the therapies used is not given in detail; – Lack of detailed baseline patient characteristics for the compared arms; – No information on inclusion/exclusion criteria; – There are no results on the use of methylprednisolone in the general study population and the non-ARDS study subpopulation

Results						
Outcome	**Observation time**	**Intervention**	**Control**	**Relative parameter HR (95% CI)**	**NNT**	**Clinical relevance**
Death [n/N], (%)	NDA	23/50 (46.0%)	21/34 (61.8%)	**^0.38 (0.20; 0.72)**	**6 (3; 18)***	
The use of methylprednisolone may be beneficial in the treatment of patients with ARDS associated with COVID-19 in reducing the mortality risk.						

^Data from the publication; *AOTMiT's own calculations

Table 14. Description of the methodology and results of Wu 2020b

Wu 2020b						
Systemic corticosteroids show no benefit in severe and critical COVID-19 patients in Wuhan, China: A retrospective cohort study						
Methodology	**Population**		**Intervention**	**Control**	**Standard clinical practice**	**Limitations**
Retrospective, two-centre cohort study Duration of the study: Patients admitted between 26/12/2019 and 15/03/2020 Observation until 19/03/2020	N= 1 763 (1514 severe condition*, 249 critical condition**) Patients with laboratory-confirmed or clinically-confirmed COVID-19 Exclusion criteria: no severe or critical condition; no severe condition within 24 hours of admission to hospital; no data on time from diagnosis to severe/critical condition		Ni= 690 patients (531 severe condition, 159 critical condition) i.v. glucocorticoids (5 mg hydrocortisone or 1 mg methylprednisolone or 0.1875 mg dexamethasone) + SoC	Nc= 1,073 patients (983 severe condition, 90 critical condition) Glucocorticoids not used SoC	There is no established COVID-19 procedure in Poland	– No detailed information on the standard of care used; – Statistically significant differences in the baseline characteristics of patients in the arm receiving corticosteroids in the severe subpopulation, higher percentage of elderly patients; significant differences in laboratory parameters in both subpopulations compared to the control arm
	Severe condition	Age, years^	63 (53-71)	60 (50-69)		
		Women (%)^	240 (45.2)	550 (56)		
	Critical condition	Age, years	68 (60-75)	67 (54-82)		
		Women (%)	65 (40.9)	37 (51.1)		

Results							
Outcome		**Observation time**	**Intervention**	**Control**	**Relative parameter (95% CI) / p^^**	**NNT**	**Clinical relevance**
Death [n/N] (%)	Severe condition, n/N (%)	NDA	83/531 (15.6)	26/983 (2.6)	**HR=1.77 (1.08; 2.89)** HR=1.55 (0.83; 2.87) ^^^	**7 (6; 10)#** **-**	
	Critical condition, n/N (%)		70/159 (44.0)	14/90 (15.6)	**HR=2.07 (1.08; 3.98)** **HR=2.90 (1.17; 7.16)^^^**	**3 (3; 6)#** NDA	
Duration of hospitalisation, days	Severe condition, n/N (%)		15.2 (9.1-23.8)	11.5 (6.9-17.8)	**p< 0.001**	-	
	Critical condition, n/N (%)		12.9 (5.1-21.9)	15.6 (7.9-24.5)	p=0.203	-	
Progression to critical condition, n/N (%)			149/531 (28.1)	104/983 (10.6)	**p< 0.001** **# RR=2.65 (2.11; 3.33)**	**6 (5; 7)#**	
The use of corticosteroids is not beneficial in reducing hospital mortality in severe and critical COVID-19 patients – routine use of corticosteroids is not recommended in these patients.							

*severe condition – need for oxygen therapy in the course of hospitalisation; **critical condition – throughout the entire hospitalisation, the need for mechanical ventilation, treatment in the ICU, occurrence of shock in the hospital; ^p< 0.001; ^^results from the publication; ^^^analysis taking confounders into account; # AOTMiT's own calculations;

Table 15. Description of the methodology and results of Fernandez-Cruz 2020

Fernandez-Cruz 2020						
Impact of glucocorticoid treatment in SARS-CoV-2 infection mortality: a retrospective controlled cohort study						
Methodology	**Population**		**Intervention**	**Control**	**Standard clinical practice**	**Limitations**
Single-centre retrospective study Duration of the study: 4/03-7/04/2020 To minimise the influence of confounding factors, the analysis of the results included the propensity score, separately for the comparison of the arm receiving and not receiving glucocorticoids, and for the type of GCs administration.	N=463 Patients with laboratory-confirmed SARS-CoV-2 infection and/or hyperinflammatory syndrome		Ni=396 Glucocorticoids: - methylprednisolone 1 kg / day (78.3% of patients, 22.5% of whom were administered pulsatile glucocorticoids) - GCs (pulse administration) (21.7%): <250 mg / d (20.1%), 250 mg / d (62.5%) and 500 mg / d (17.1%).	Nc=67 No GCs therapy	There is no established COVID-19 procedure in Poland	– Single-centre, retrospective study; – There are differences in the baseline characteristics of patients – significantly more people in the arm not receiving glucocorticoids suffered from oncohaematological disorders and peptic ulcer disease; – There was a significantly longer time from symptom onset to diagnosis in the GCs arm; – Patients in the GCs arm took hydroxychloroquine and tocilizumab significantly more often, and other therapies were administered less frequently.
	Age, mean (SD)		65.4 (12.9)	68.1 (15.7)		
	Men (%)		69.7	61.2		
	Coexisting conditions (%)	Total	77.3	79.1		
		Hypertension	46.0	47.8		
		Coronary heart disease	18.2	17.9		
		Diabetes	21.2	19.4		
		Obesity	7.3	9.0		
		Dyslipidaemia	28.5	32.8		
		Chronic kidney diseases	6.1	6.0		
		Onco-haematological diseases	12.4	23.9		
		Neurological diseases	8.8	16.4		
		Immunosuppression diseases	9.3	6.0		
		Ulcers	0.8	4.5		
	Other therapies (%)	Hydroxychloroquine	99.5	92.5		
		Lopinavir/ritonavir	73	62.7		
		Azithromycin	53.9	43.9		
		Interferon	47.2	41.8		
		Tocilizumab	44.9	18.5		
		Other therapies**	16.4	29.9		
	Time from symptom onset to diagnosis, days (SD)		8.5 (5.1)	6.9 (3.9)		

Fernandez-Cruz 2020					
	Median time from onset of symptoms to hospital admission, days (SD)	7.6 (4.2)	7.0 (3.7)		
	Time from symptom onset to treatment initiation, days (SD)	7.4 (4.1)	7.1 (3.6)		

Results							
Outcome		**Observation period (days)**	**Intervention**	**Control**	**Relative parameter (95% CI)**	**Absolute NNT parameter (95% CI)**	**Clinical relevance**
In-hospital mortality	Total	NDA	55/396 (13.9%)	16/67 (23.9%)	**HR=0.51 (0.27; 0.96)**	**10 (4;129)^**	
	Patients with severe of moderate ARDS		26.2%	60%	OR=0.23 (0.08; 0.71)	-	
Steroid treatment reduced mortality by 41.8% compared to lack of steroid treatment (RRR 0.42 (95%CI: 0.048; 0.65)). Initial methylprednisolone treatment at a dose of 1 mg / kg / day compared to pulsatile steroids was not associated with in-hospitals mortality (13.5% [42/310] compared to 15.1% [13/86], OR=0.880 (95%CI: 0.449; 1.726), p = 0.71.							
Results of the study indicate that survival of patients with SARS-CoV2-caused pneumonia is greater in patients receiving GCs than other patients. In-hospital mortality between the initial treatment regimens with methylprednisolone at a dose of 1 mg / kg / day and pulsatile glucocorticoids did not differ.							
* In cases when during hospitalisation, the patient received different glucocorticoids, the first regimen was included in the analysis; ** including ritonavir + darunavir, clarithromycin, doxycycline and other antibiotics; ^ AOTMiT's own calculations ARDS – acute respiratory distress syndrome							

Table 16. Description of the methodology and results of Albani 2020

Albani 2020					
Effect of Corticosteroid Treatment on 1376 Hospitalized COVID-19 Patients. A Cohort Study					
Methodology	**Population**	**Intervention**	**Control**	**Standard clinical practice**	**Limitations**
Retrospective, single-centre cohort study Duration of the study: Patients admitted between 20/02/2020 and 10/05/2020 Observation until 19/03/2020	N= 1,443 Patients with RT-PCR laboratory - confirmed SARS-CoV-2 infection Exclusion criteria: age <18 years; results unavailable at the time data was analysed	Ni = 559 patients Glucocorticoids (dexamethasone 8 mg or its equivalent in the form of hydrocortisone or methylprednisolone) + SoC	Nc = 844 patients Glucocorticoids not used SoC	There is no established COVID-19 procedure in Poland	– No detailed information on the standard of care used; – Statistically significant differences in the baseline patient characteristics, including arterial hypertension and BMI higher in the corticosteroid arm; statistically significant differences in laboratory parameters; – Significant impact of confounding factors on the analysis results; – Single-centre study
	Age, years	68.7 (11.5)	68.5 (15.1)		
	Women (%)	193 (34.5)	286 (33.9)		
	BMI*	27.3 (4.9)	26.4 (5.0)		
	Hypertension (%)*	218 (39.0)	281 (33.3)		
	$Pa0_2$*	53.2 (18.5)	59.9 (23.8)		
	$Pa0_2$/ $Fi0_2$*	235.2 (74.6)	269.0 (75.1)		

Results						
Outcome	**Observation time**	**Intervention**	**Control**	**Relative parameter OR (95% CI)**	**NNT**	**Clinical relevance**
Deaths [n/N] (%)	NDA	171/559 (30.6)	183/844 (21.7)	**^1.57 (1.23; 2.01)** ^1.15 (0.90; 1.45)^^	**11 (8; 24)*** -	
Transfer to the ICU, [n/N] (%)		56/559 (11.5)	131/844 (14.4)	^0.77 (0.55; 1.07) **^0.48 (0.34; 0.66)^^**	- **18 (11; 50)***	
In the analysis taking into account factors confounding, the use of corticosteroids does not impact in-hospital mortality. Possible benefits of using corticosteroids associated with reduction of admissions to the ICU.						

* Statistically significant differences; * AOTMiT's own calculations; ^ results from the publication; ^^ analysis taking confounders into account;

Table 17. Description of the methodology and results of Bani-Sadr 2020

Bani-Sadr 2020					
Corticosteroid therapy for patients with COVID-19 pneumonia: a before–after study					
Methodology	**Population**	**Arm 1**	**Arm 2**	**Standard clinical practice**	**Limitations**
Retrospective – *before and after study,* single-centre Duration of the study: 03/03/2020 to 14/04/2020 Analysis of data from two periods – before and after initiation of corticosteroid treatment in addition to standard of care in the hospital (period I: 03/03-20/03 period II: 26/03-14/04/2020)	N= 257 Patients with COVID-19 Inclusion criteria: RT-PCR- or CT-confirmed COVID-19. Exclusion criteria: patients initiating corticosteroid treatment in the transition period (21-25/03); patients with symptom onset <7 days.	Ni= 172 patients, of which 119 used corticosteroids Methylprednisolone or prednisone (equivalent of 1 mg/kg or 0.5 mg/kg if additional antiviral RTV treatment is used.) SoC	Nc= 85 patients, of which 11 used corticosteroids SoC (antiviral treatment, antibiotic therapy, HCQ/CQ, anticoagulants)	There is no established COVID-19 procedure in Poland	– Uneven distribution of patients in the study and control arms; – It is not possible to compare the baseline characteristics of patients treated with and not treated with corticosteroids – the characteristics presented apply to all patients treated in the indicated periods, some patients in period I received corticosteroids, while in period II not all patients received corticosteroids; – Different baseline patient characteristics in the compared arms; – Short duration of the study; – Single-centre study
	Age, years – median (IQR):	71.8 (69.2)	70.1 (15.1)		
	Men, n (%):	89 (51.7)	46 (54.1)		
	Time from symptom onset to hospital admission, days (SD)*	7.5 (4.9)	5.8 (4.2)		
	Heart conditions, n (%)	94 (54.7)	41 (48.2)		
	Chronic disease of the respiratory system, n (%)	32 (18.6)	22 (25.9)		

Results						
Outcome	**Observation time**	**Intervention**	**Control**	**Relative parameter (95% CI)**	**NNT**	**Clinical relevance**
Mortality ratio, n/N (%)	Median: 16±7 days	NDA	NDA	^HR=0.86 (0.47; 1.56)^^ **^HR=0.47 (0.23; 0.97)^^^**	NDA	
		31/172 (18)	17/85 (20)	OR=0.88 (0.46; 1.70)*	-	
Rate of admissions and/or deaths before admission to the ICU, n (%)		NDA	NDA	^HR=0.25 (0.11; 0.55)^^ **^HR=0.37 (0.21; 0.64)^^^**	NDA	
		40/172 (23.6)	29/85 (34.1)	OR=0.59 (0.33; 1.04)*	-	
Conclusions of the authors of the study: The addition of corticosteroids to the inpatient COVID-19 treatment regimens is associated with a significant reduction in hospital mortality.						

* Statistically significant differences; ^ data from the publication; ^^ non-adjusted analysis; ^^^ multivariate analysis taking age into account, NEWS, institutional status; * AOTMiT's own calculations

Table 18. Description of the methodology and results of Feng 2020

Feng 2020							
COVID-19 with Different Severities: A Multicenter Study of Clinical Features							
Methodology	**Population**		**Intervention**	**Control**	**Standard clinical practice**	**Limitations**	
Retrospective, multi-centre cohort study Duration of the study: 01/01/2020 to 15/02/2020 Analysis for the sub-population using corticosteroids	N= 476 patients (moderate n=352, or severe n=54, critical n=70) Patients with diagnosed COVID-19 Age, years – median (IQR): 53 (40-64) Men: 56.9% Inclusion criteria: meeting diagnostic criteria in line with edition 5 of *Guidelines on the Diagnosis and Treatment of COVID-19* developed by the *National Health Commission of China*.		Ni = 75 patients Glucocorticoids (no detailed data) + SoC	Nc = 331 patients Glucocorticoids not used SoC	There is no established COVID-19 procedure in Poland	– No detailed information on the use of corticosteroids (dosage, drugs) and standard of care is available; – No data for comparing the baseline characteristics of the study and control patients are available; – No data on the duration of treatment are available	
Results							
Outcome		**Observation time**	**Intervention**	**Control**	**Relative parameter (95% CI) / p**	**NNT**	**Clinical relevance**
Duration of hospitalisation, days	Moderate or severe condition	NDA	22 (17-32)	15 (11-22)	**^p<0.001**	-	
Death, n/N (%)	Critical condition		21/52 (40.4)	8/18 (44.4)	**^p=0.013**	-	
Hospital discharge, n/N (%)			13/52 (25)	10/18 (55.6)			
Disease progression (need for mechanical ventilation or death)			42/52 (80.8)	18/18 (100)	^p=0.054	-	
Conclusions of the authors of the study: in moderate or severe patients, the use of corticosteroids can be associated with longer hospitalisation.							

^ results from the publication

Table 19. Description of the methodology and results of Shang 2020

Shang 2020							
The treatment and outcomes of patients with COVID-19 in Hubei, China: a multicentered, retrospective, observational study							
Methodology	**Population**		**Intervention**	**Control**	**Standard clinical practice**	**Limitations**	
Retrospective, multi-centre cohort study Duration of the study: 27/12/2019 to 17/02/2020 Analysis for the corticosteroid-using subpopulation of survivors	N= 416 Patients with COVID-19 Researchers divided population according to disease severity: severe or critical, or non-severe / critical. Severe or critical / other conditions - age, median (IQR): 50 (38-60) / 46 (33-56); - male: 55% / 39%; - comorbidities: 50% / 23%; - number of days from symptom onset to hospitalisation, median (IQR): 9 (6-11) / 6 (4-8); - hospitalisation time, median (IQR): 12 (9-16) / 10 (7-13). Inclusion criteria: COVID-19 diagnosed in line with the *New Coronavirus Infected Pneumonia* Diagnosis and Treatment Plan (Trial Version 6), National Health Committee of the People's Republic of China criteria		Ni = 76/226 non-severe/critical patients and 77/139 severe/critical patients used corticosteroids Glucocorticoids: (prednisone, methylprednisolone, dexamethasone) Dose mg / day, median (IQR) – severe/critical: 38.7 (29.7-46.2), other than severe/critical: 40 (34.2-40); SoC	Ni = 150/226 non-severe/critical patients and 62/139 severe/critical patients used glucocorticoids SoC (including LPV / RTV, oseltamivir, arbidol, interferon, antibiotics)	There is no established COVID-19 procedure in Poland	– There is no possibility to compare the baseline characteristics of patients from intervention and control groups – the presented characteristics of patients apply to all patients in the analysed conditions, regardless of the treatment used; – The aim of the study was not to analyse the therapeutic effect of corticosteroids.	
Results							
Outcome		**Therapy duration, days (IQR)**	**Intervention**	**Control**	**Relative parameter (95% CI) / p**	**NNT**	**Clinical relevance**
Duration of hospitalisation, days (IQR)	Critical/severe condition	8 (5.5-11)	14 (10-18)	11 (9-13)	**p<0.05**	-	
	Other conditions	6 (4-9)	12 (9-16)	10 (8-13)	**p<0.05**	-	
Conclusions: the use of corticosteroids extends hospitalisation time in both severely/critically ill and in other conditions case of patients with COVID-19.							

Table 20. Description of the methodology and results of Lu 2020

<table>
<tr><th colspan="7">Lu 2020</th></tr>
<tr><th colspan="7">Adjuvant corticosteroid therapy for critically ill patients with COVID-19</th></tr>
<tr><th>Methodology</th><th>Population</th><th>Intervention</th><th>Control</th><th>Standard clinical practice</th><th colspan="2">Limitations</th></tr>
<tr><td>A: Retrospective cohort study
B: 1:1 matched case-control study

All corticosteroid doses have been converted to equivalent hydrocortisone doses.

Hospital admission: 25/01 - 25/02/2020
Country: China</td><td>N=244
Patients who are critically ill with COVID-19

Inclusion criteria: critically ill patients with laboratory confirmed SARS-CoV-2 (defined as admission to the ICU and requiring mechanical ventilation (invasive or non-invasive), or patients with ARDS, sepsis with organ failure); age ≥ 20 years, prior antiviral therapy.

Study A:
N_A=244
Median age (IQR) = 62 (50-71) years
Men: 52%
Dyspnoea: 60%
ARDS: 36%
<u>Differences in the characteristics of the assessed groups (GCs vs no-GCs):</u>
<u>- in patients in the GCs group, organ dysfunction was more common</u>

Study B:
N_B=62
31 pairs of patients were selected based on the propensity score matching score for the identified potential confounding factors. A balanced distribution of patients' characteristics was obtained in the matched pairs (p> 0.05)</td><td>Glucocorticoids as adjuvant treatment after antiviral therapy:
Dose: equivalent to 100-800 mg/day of hydrocortisone
Median duration of treatment (IQR): 8 (4-12) days</td><td>No glucocorticoids</td><td>There is no established COVID-19 procedure in Poland</td><td colspan="2">– Retrospective analysis of medical records;
– No detailed results for the number of events</td></tr>
<tr><td></td><td></td><td colspan="2">All patients received antiviral treatment (including: oseltamivir, arbidol, lopinavir/ritonavir, ganciclovir; interferon alpha)</td><td></td><td colspan="2"></td></tr>
<tr><td></td><td></td><td colspan="2">Study A</td><td></td><td colspan="2"></td></tr>
<tr><td></td><td></td><td>Ni=151</td><td>Nc=93</td><td></td><td colspan="2"></td></tr>
<tr><td></td><td></td><td colspan="2">Study B</td><td></td><td colspan="2"></td></tr>
<tr><td></td><td></td><td>Ni=31</td><td>Nc=31</td><td></td><td colspan="2"></td></tr>
<tr><td colspan="7">Results</td></tr>
<tr><th colspan="2">Outcome</th><th>Observation time (days)</th><th>Intervention</th><th>Control</th><th>OR (95%CI) / p</th><th>Absolute parameter</th><th>Clinical relevance</th></tr>
<tr><td colspan="8">Study A</td></tr>
<tr><td colspan="2">Mortality</td><td>28 days**</td><td>NDA</td><td>NDA</td><td>1.05 (0.15; 7.46); ^p>0.3</td><td>-</td><td></td></tr>
<tr><td colspan="8">Study B</td></tr>
<tr><td colspan="2">Mortality, n (%)</td><td>28 days**</td><td>12/31 (39%)</td><td>5/31 (16%)</td><td>p=0.09
p=0.17^^</td><td>-</td><td></td></tr>
<tr><td colspan="8">Increased corticosteroid dosage was significantly associated with elevated mortality risk after adjustment for administration duration (P = 0.003); every 10-mg increase in dosage was associated with additional 4% mortality risk: HR = 1.04 (95%CI: 1.01-1.07) p=0.003</td></tr>
</table>

**28 days after administration (GCs group) / admission to the ward (no-GCs group); ^ multivariate logistic regression; ^^analysis stratified by adjuvant corticosteroid treatment

Table 21. Description of the methodology and results of Majmundar 2020

Majmundar 2020					
Efficacy of Corticosteroids in Non-Intensive Care Unit Patients with COVID-19 Pneumonia from the New York Metropolitan region					
Methodology	**Population**	**Intervention**	**Control**	**Standard clinical practice**	**Limitations**
Retrospective, single-centre cohort study Duration of the study: from 16/03/2020 to 30/04/2020	N= 205 patients Patient with COVID-19 (according to WHO criteria). Inclusion criteria: 1) Age ≥ 18 years old, 2) Confirmed cases of SARS-CoV-2 by PCR method, 3) Admitted in general wards, 4) PaO2/FiO2 (PF) ratio <300 if Arterial blood gas if available or SpO2/Fio2 (SF) ratio <440, 5) Bilateral infiltrate on chest imaging by radiology staff. Exclusion criteria: 1) Patients with severe immunosuppression (HIV infection, long term use of immunosuppressive agents), 2) Pregnant woman or Lactation period, 3) Oral glucocorticoids were needed for other diseases, 4) Direct admission to intensive care unit (ICU), 5) if had any of primary composite outcome within first 24 hours of admission, 6) Patient who never required oxygen during the hospital course	Ni = 60 patients Glucocorticoids: methylprednisolone (n = 29), prednisone (n = 10), hydrocortisone (n = 1), dexamethasone (n = 20). Corticosteroid was commenced at a median of 2 days (IQR, 1-5) following admission, on a median dose of 80 mg (IQR, 60-107) of methylprednisolone or its equivalent. + SoC	Nc = 145 patients No glucocorticoids +SoC	There is no established COVID-19 procedure in Poland	– Statistically significant differences in the baseline characteristics of patients; – Treatment of tocilizumab and enoxaparin was significantly more frequent than in the group of patients not taking corticosteroids (18.33 vs 4.83%, p = 0.002 and 66.67 vs 24.83%, p <0.001) – No detailed information on the standard of care used; – No information about the loss of patients in the study and control groups in the analysis for individual Outcomes; – Single-centre study; – Pre-print status.
	Age, years (SD)	58.7 (13.35)	57.18 (16.81)		
	Men (%)	(86.7)	(69.97)		
	Obesity*	(46.8)	(30.5)		
	Pa02/ Fi02, median (IQR)*	136.4 (65.2-218.97)	261.9 (219.0-280.95)		
	Sp02/ Fi02, median (IQR)*	190 (92.5-298.4)	339.3 (278.1-419.1)		

Results						
Outcome	**Observation time**	**Intervention**	**Control**	**Relative parameter (95% CI)**	**NNT**	**Clinical relevance**
ICU transfer, intubation or death, n (%) N=202	Median duration of treatment 5 days (IQR, 4-7)	13/NDA (22.41%)	54/NDA (37.5%)	**HR*=0.15 (0.07; 0.33)^** **HR*=0.45 (0.24; 0.82)^^**	-	
Discharge from hospital, n (%) N=191		47/NDA (85.45%)	102/NDA (75%)	**HR*=3.65 (2.20; 6.06)^** HR*=1.17 (0.83; 1.65)^^	-	
Death, n (%) N=191		8/NDA (14.55%)	34/NDA (25%)	HR 0.53* (0.22;1.31)^ HR*=0.62 (0.29; 1.35)^^	-	
Intubation, n (%) N=200		11/NDA (18.97%)	36/NDA (25.35%)	**HR*=0.31 (0.14; 0.70)^** HR*=0.66 (0.33; 1.29)^^	-	
ICU transfer, n (%) N=202		12/NDA (20.69%)	47/NDA (32.64%)	**HR*=0.16 (0.07; 0.34)^** **HR*=0.49 (0.26; 0.93)^^**	-	
Duration of hospitalisation, days (IQR) =191		9/ND (6-17)	7/ND (5-13)	-1.06 (-4.26; +2.14) p=0.52^ 1.15 (-1.61; +3.92) p=0.41^^	-	
Among non-ICU patients hospitalised with COVID-19 pneumonia complicated by AHRF, treatment with corticosteroid was associated with a significantly lower risk of the primary composite outcome of ICU transfer, intubation, or in-hospital death.						

* statistically significant differences; ^ adjusted; ^^ unadjusted;

Table 22. Description of the methodology and results of Li 2020

Li 2020					
Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan					
Methodology	**Population**	**Intervention**	**Control**	**Standard clinical practice**	**Limitations**
Retrospective, single-centre, cohort study Duration of the study: Patients admitted between 26/01/2020 and 05/02/2020 Observation until 03/03/2020 Analysis for the sub-population using corticosteroids	N= 548 patients (severe: n=269, non-severe: n=279) Patients with COVID-19 Median age, years (IQR): 60 (48-69) Men: 50.9% Inclusion criteria: meeting WHO diagnostic criteria in line with edition 5 of *Guidelines on the Diagnosis and Treatment of COVID-19* developed by the *National Health Commission of China*.	Ni= 341/548 patients Glucocorticoids (average dose of corticosteroids equivalent to 200 mg of prednisone) low dose (ld): max dose <1 mg/kg/day of prednisone high dose (hd): ≥1 mg/kg/day pf prednisone) + SoC	Nc= 207 patients* Glucocorticoids not used SoC	There is no established COVID-19 procedure in Poland	– No data to compare baseline characteristics of patients from the study and control group; – No data on the number of high and low dose corticosteroid users and the number of events; – Short follow-up; – The aim of the study was to analyse risk factors, not treatment effectiveness; – Single-centre study

Results								
Outcome		**Therapy duration**	**Intervention**		**Control**	**Relative parameter HR (95% CI)**	**NNT**	**Clinical relevance**
Death during hospitalisation	Severe patients (n=279)	Median: 4 days	**High dose**	NDA	NDA	**3.5 (1.8;6.9)^ 3.32 (1.85; 5.97)^^**	NDA	
			Low dose	NDA	n/d	1.26 (0.61;2.58)^ 1.07 (0.57; 2.01)^^	NDA	
Conclusions: in patients with a severe condition associated with COVID-19, use of high doses of corticosteroids may be associated with an increased mortality risk. When interpreting results, using high doses of corticosteroids, especially in patients with deteriorating health, should be taken into account.								

*Agency's own calculation; ^ adjusted; ^^ unadjusted

Table 23. Description of the methodology and results of Zhou 2020

Zhou 2020					
Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study					
Methodology	**Population**	**Intervention**	**Control**	**Standard clinical practice**	**Limitations**
Retrospective cohort study, multi-centre Duration of the study: from 29.12.2019 to 31.01.2020.	N=191 Patients with SARS-CoV-2 confirmed by RT-PCR (according to WHO) Age: 56 (46-67) Men: 62% Critical status: 53 (28%) Severe status: 66 (35%) Time from illness onset to hospital admission: 11 (8-14) Inclusion criteria: - patients with SARS-CoV-2 confirmed by RT-PCR ≥ 18 years of age - patients who had a definite outcome (dead or discharged) at the early stage of the outbreak	Ni=57 Glucocorticoids (no specific data available) SoC: antibiotics (95%), antiviral treatment (21%), immunoglobulin (24%),	Nc=134* other treatments that do not include glucocorticoids	There is no established COVID-19 procedure in Poland	– The dosage of used therapies was not reported; – Patient observation time was not reported; – There was no stratification, e.g. by type and dose of GCs; – No data to compare baseline characteristics of patients from the study and control group; – Ambiguous presentation of results

Results						
Outcome	**Observation time**	**Intervention**	**Control**	**Relative parameter OR (95% CI)**	**NNT**	**Clinical relevance**
Death [n/N], (%)	NDA	26/57 (45.6)	31/134 (23.1)	**2.79 (1.44;5.38)**	**4 (3; 13)***	
There is no evidence of a benefit of glucocorticoid use in adult patients with COVID-19.						

* Agency's own calculations

Table 24. Description of the methodology and results of Sanz Herrero 2020

Sanz Herrero 2020					
Methylprednisolone added to tocilizumab reduces mortality in SARS-CoV-2 pneumonia: An observational study					
Methodology	**Population**	**Intervention**	**Control**	**Standard clinical practice**	**Limitations**
Retrospective, single-centre study Duration of the study: NDA Analysis of data from two periods - before and after inclusion of corticosteroids for standard hospital treatment (cut-off date 03/27/2020)	N= 72 Patients with SARS-CoV-2 confirmed by RT-PCR. Inclusion criteria: PaO2/FiO2<300, SpO2<92 (room air), tachypnoea, and high ferritin levels	Ni = 56 patients Methylprednisolone 250 mg i.v. daily on the first day followed by 40 mg every 12h for 4 more days and stopped without tapering) + tocilizumab (400 mg single dose) + SoC (HCQ+AZM - 94.6%, LPV/RTV - 80.4%, IFN-β - 25% patients)	Nc = 16 patients Tocilizumab (single 400 mg dose) + SoC (HCQ+AZM – 93.8%, LPV/RTV - 81.3%, IFN-β - 62.5 % patients)	There is no established COVID-19 procedure in Poland	– Unequal distribution of patients in the study and control groups – Differences in the baseline characteristics of patients from the compared arms, in the control group, statistically significantly more patients used interferon beta; – Short follow-up; – Single-centre study
	Age, years – median (IQR)	67 (61-76.8)	68.9 (60.8-78.3)		
	Men (%)	33 (58.9)	12 (75)		
	Hypertension (%)	31 (55.4)	12 (75)		
	Diabetes (%)	12 (21.4)	7 (43.8)		

Results						
Outcome	**Observation time**	**Intervention**	**Control**	**Relative parameter RR (95% CI) / p**	**NNT**	**Clinical relevance**
Death, n (%)	NDA	11/56 (19.6)	10/16 (62.5)	**^0.20 (0.08; 0.47)**	**2 (2; 6)***	
Duration of hospitalisation, days		17.5 (15-20)	12.6 (3.5-22.5)	**^p=0.028**	-	
Duration of hospitalisation in survivors, days		18.8 (15.5-21)	23.2 (16.5-28.3)	^p=0.091	-	
Transfer to the ICU, n (%)		31/56 (55.4)	12/16 (75)	^p=0.158	-	
Median duration of viral shedding, n (%)		19.5 (13.4-28)	21.5 (16-30.3)	^p=0.713	-	
In patients with maximised treatment, who are also especially severe and some with distress criteria, the administration of corticosteroids improved survival.						

^ data from publication; * AOTMiT's own calculations

Table 25. Search strategies for PubMed and Embase (date of search: 27-28/07/2020)

Pubmed (27/07/2020)	**Results**
((((corticosteroid*) OR (glucocorticoid*)) OR (prednisone OR prednisolone OR methylprednisolone OR dexamethasone)) OR (hydrocortisone OR cortisone OR ethamethasoneb OR triamcinolone OR bethamethasone)) AND ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "COVID-19"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2" OR COVID-19 OR "COVID 19" OR COVID19 OR SARS-CoV-2 OR "SARS CoV 2" OR "SARS-CoV 2" OR "SARSCoV 2" OR "SARS CoV-2" OR "SARS CoV2" OR SARS-CoV2 OR SARSCoV-2 OR SARS2 OR "SARS 2" OR SARS-2 OR 2019-nCoV OR "2019 nCoV" OR "nCoV 2019" OR "nCoV-2019" OR 2019nCoV OR "2019 novel coronavirus" OR "coronavirus disease 2019" OR "coronavirus disease-19" OR "novel coronavirus pneumonia" OR "novel coronavirus disease" OR "novel coronavirus infected pneumonia" OR "Wuhan coronavirus" OR "Wuhan seafood market pneumonia virus" OR "2019-novel coronavirus" OR "2019 new coronavirus" OR "2019-new coronavirus" OR "coronavirus disease-2019" OR SARSCoV2) Filters: English, Polish	342
Embase (28.07.2020 r.)	
(corticosteroids or glucocorticoids or prednisone or prednisolone or methylprednisolone or dexamethasone or hydrocortisone or cortisone or triamcinolone or bethamethasone).ab. and ("severe acute respiratory syndrome coronavirus 2" or COVID-19 or "COVID 19" or COVID19 or SARS-CoV-2 or "SARS CoV 2" or "SARS-CoV 2" or "SARSCoV 2" or "SARS CoV-2" or "SARS CoV2" or SARS-CoV2 or SARSCoV-2 or SARS2 or "SARS 2" or SARS-2 or 2019-nCoV or "2019 nCoV" or "nCoV 2019" or "nCoV-2019" or 2019nCoV or "2019 novel coronavirus" or "coronavirus disease 2019" or "coronavirus disease-19" or "novel coronavirus pneumonia" or "novel coronavirus disease" or "novel coronavirus infected pneumonia" or "Wuhan coronavirus" or "Wuhan seafood market pneumonia virus" or "2019-novel coronavirus" or "2019 new coronavirus" or "2019-new coronavirus" or "coronavirus disease-2019" or SARSCoV2).ti.	228

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