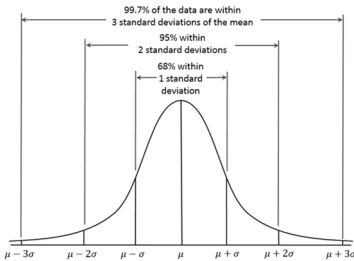


Dexametason vid Covid-19

Standardavvikelse (standard deviation, SD):
Vanligt spridningsmått tillsammans med medelvärdet.
För en normalfördelad variabel ligger 68% av alla värden inom \pm en standardavvikelse från medelvärdet.

95% av alla värden ligger inom ± 2 (1.96) standardavvikelse från medelvärdet.

<https://www.students4bestevinden.ce.net/blog/2018/09/26/a-beginners-guide-to-standard-deviation-and-standard-error/>



Beskrivande statistik och statistisk inferens

Artikeln ger beskrivande statistik (medelvärde och standardavvikelse, SD) för studiepopulationernas (stickprovens) ålder:

Dexametason (n=2104): 66.9 ± 15.4
Standard beh (n=4321): 65.8 ± 15.8

Vi kan använda dessa data för att dra slutsatser (statistisk inferens) om medelåldern för de två populationer som stickproven är tagna från (medelålder och standard error, $se = SD/\sqrt{n}$, n=antal observationer):

Dexametason (n=2104): 66.9 ± 0.34
Standard beh (n=4321): 65.8 ± 0.24

Beskrivande statistik och statistisk inferens

Standard error (se) beskriver osäkerheten i uppskattningen av populationens medelvärde, det motsvarar standardavvikelsen i den fördelning av medelvärden man skulle få om man gör många stickprov av det slag som i artikeln. Liksom tidigare ligger 68% av alla sådana medelvärden inom \pm en standardavvikelse (se). 95% av alla sådana medelvärden ligger inom ± 1.96 se. Kan användas för att beräkna 95% konfidensintervall (CI):
Dexametason (n=2104): 66.9 (95%CI 66.2-67.6)
Standard beh (n=4321): 65.8 (95%CI 65.3-66.3)

Även om 95%CI överlappar (något lite) kan skillnaden mellan grupperna vara statistiskt signifikant.

Beskrivande statistik och statistisk inferens

Unpaired t test results

P value and statistical significance:
The two-tailed P value equals 0.0083
By conventional criteria, this difference is considered to be very statistically significant.

Confidence interval:
The mean of Group One minus Group Two equals 1.100
95% confidence interval of this difference: From 0.282 to 1.918

Intermediate values used in calculations:
t = 2.6406
df = 6423
standard error of difference = 0.417

Learn more:
GraphPad's web site includes portions of the manual for GraphPad Prism that can help you learn statistics. First, review the meaning of **P values** and **confidence intervals**. Then learn how to interpret results from an **unpaired** or **paired** t test. These links include GraphPad's popular **analysis checklists**.

Review your data:

| Group | Group One | Group Two |
|-------|-----------|-----------|
| Mean | 66.900 | 65.800 |
| SD | 15.400 | 15.800 |
| SEM | 0.336 | 0.240 |
| N | 2104 | 4321 |

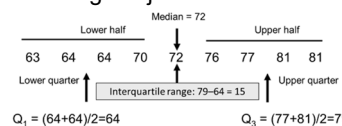
<https://www.graphpad.com/quickcalcs/ttest2/>

| Characteristic | Treatment Assignment | | Respiratory Support Received at Randomization | |
|---|------------------------|---------------------|---|---|
| | Dexamethasone (N=2104) | Usual Care (N=4321) | No Receipt of Oxygen (n=1510) | Oxygen or Mechanical Ventilation (n=1885) |
| Age† | | | | |
| Mean—yr | 66.9±15.4 | 65.8±15.8 | 69.4±17.5 | 66.7±15.3 |
| SD | 15.4 | 15.8 | 17.5 | 15.3 |
| Distribution—no. (%) | | | | |
| <70 yr | 1141 (54) | 2504 (58) | 459 (49) | 2148 (55) |
| 70 to 79 yr | 489 (23) | 859 (20) | 138 (15) | 721 (22) |
| ≥80 yr | 474 (23) | 958 (22) | 533 (56) | 425 (13) |
| Sex—no. (%) | | | | |
| Male | 1138 (54) | 2149 (50) | 616 (65) | 1463 (55) |
| Female | 766 (36) | 1572 (36) | 444 (44) | 1422 (45) |
| Median no. of days since symptom onset (IQR)‡ | 8 (5–13) | 9 (5–13) | 4 (3–10) | 9 (5–12) |
| Median no. of days since hospitalization (IQR)‡ | 2 (1–5) | 2 (1–5) | 2 (1–4) | 5 (3–9) |
| Respiratory support received—no. (%) | | | | |
| No support | 565 (27) | 1034 (24) | 1570 (100) | NA |
| Oxygen only | 1279 (61) | 2604 (60) | NA | 1883 (100) |
| Invasive mechanical ventilation | 324 (15) | 483 (11) | NA | NA |
| Previous comorbid disease | | | | |
| Any | 565 (27) | 1034 (24) | 911 (59) | 2175 (56) |
| Diabetes | 123 (6) | 1821 (42) | 342 (22) | 959 (24) |
| Heart disease | 386 (18) | 1175 (27) | 525 (34) | 1075 (28) |
| Chronic lung disease | 415 (20) | 933 (21) | 351 (23) | 883 (23) |
| Tuberculosis | 6 (0) | 19 (0) | 8 (0) | 11 (0) |
| Hypertension | 122 (6) | 261 (6) | 5 (0) | 21 (0) |
| Severe liver disease§ | 37 (2) | 82 (2) | 32 (2) | 72 (2) |
| Severe kidney impairment¶ | 166 (8) | 358 (8) | 119 (8) | 251 (7) |
| SARS-CoV-2 test result | | | | |
| Positive | 1850 (88) | 3648 (84) | 1137 (75) | 3418 (88) |
| Negative | 247 (12) | 483 (11) | 373 (25) | 467 (12) |
| Test result not yet known | 7 (0) | 29 (0) | 9 (0) | 15 (0) |

* Also-missing values are means ±SD. HIV denotes human immunodeficiency virus; IQR, interquartile range; NA, not applicable; and SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
† There was a significant (P<0.05) difference in the mean age between patients in the dexamethasone group and those in the usual care group, but there was no significant difference between the groups in any other baseline characteristic.
‡ Included in this category were pregnant women.
§ Severe liver disease was defined as requiring ongoing therapy.
¶ Severe kidney impairment was defined as an estimated glomerular filtration rate less than 30 mL per minute per 1.73 m².

Dexametason vid Covid-19

Kvartilavstånd (interquartile range, IQR):
Vanligt spridningsmått då median används som genomsnittsvärde. Observationer rangordnas från lägst till högst. Medianen är mellersta värdet (delar observationerna i två delar). Delas observationerna i fyra delar får man kvartiler. Q1 är mellersta värdet i lägre halvan av observationerna, Q2 är medianen, Q3 är mellersta värdet i övre halvan av observationerna. Kvartilavståndet är Q3-Q1. Innehåller 50% av observationerna, lägsta och högsta fjärdedelen har skalats bort.



https://sphweb.bumc.bu.edu/otlt/mph-modules/bs/bs704_summarizingdata/bs704_summarizingdata7.html

$Q_1 = (64+64)/2=64$

$Q_3 = (77+81)/2=79$

Resultat

Kaplan-Meier survival curves (eller i detta fall mortality curves).

95% konfidensintervall (95%CI): Om intervallet inkluderar 1.0 för ett förhållande (risk ratio, hazard ratio, rate ratio) är resultatet inte statistiskt signifikant.

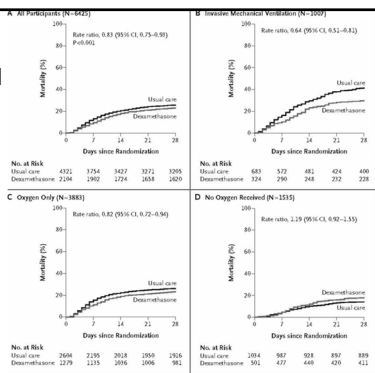


Figure 2. Mortality at 28 Days in All Patients and According to Respiratory Support at Randomization. Shows are Kaplan-Meier survival curves for 28-day mortality among all the patients in the trial (primary outcome) (Panel A) and in three respiratory support subgroups according to whether the patients were undergoing invasive mechanical ventilation (Panel B), receiving oxygen (with or without noninvasive ventilation) and without invasive mechanical ventilation (Panel C), or receiving no supplemental oxygen (Panel D) at the time of randomization. The Kaplan-Meier curves have not been adjusted for age. The rate ratios have been adjusted for the age of the patients in three categories (<70 years, 70 to 79 years, and ≥80 years). Estimates of the rate ratios and 95% confidence intervals in Panels B, C, and D were derived from a single age-adjusted regression model involving an interaction term between treatment assignment and level of respiratory support at randomization.

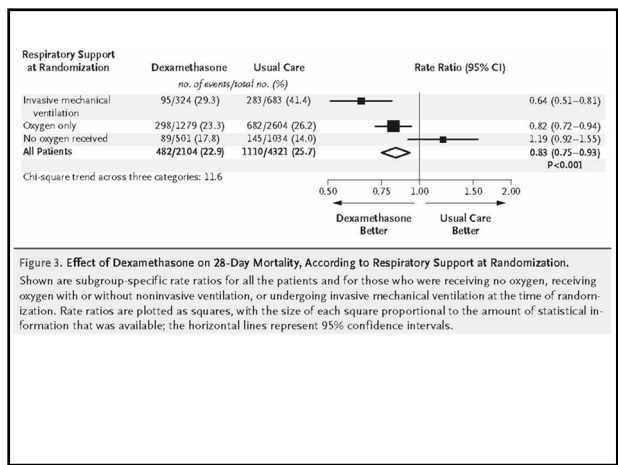


Figure 3. Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization. Shows are subgroup-specific rate ratios for all the patients and for those who were receiving no oxygen, receiving oxygen with or without noninvasive ventilation, or undergoing invasive mechanical ventilation at the time of randomization. Rate ratios are plotted as squares, with the size of each square proportional to the amount of statistical information that was available; the horizontal lines represent 95% confidence intervals.

Table S3: Impact of adjusting for the 1.1-year age imbalance between randomized arms on the estimated effect of allocation to dexamethasone on 28-day mortality, both in all randomized patients and in subgroups defined by respiratory support received at randomization

| Subgroup | no./total no. of patients (%) | | Rate ratio (95% CI) | |
|---------------------------------|-------------------------------|---------------------|------------------------------|---------------------|
| | Dexamethasone (N=2104) | Usual Care (N=4321) | Age-adjusted Cox regression* | One-step estimator† |
| No oxygen received | 89/501 (17.8) | 145/1034 (14.0) | 1.19 (0.92-1.55) | 1.30 (0.99-1.72) |
| Oxygen only | 298/1279 (23.3) | 682/2804 (24.3) | 0.82 (0.72-0.94) | 0.86 (0.75-0.99) |
| Invasive mechanical ventilation | 95/224 (29.3) | 283/683 (41.4) | 0.71 (0.51-0.81) | 0.67 (0.54-0.84) |
| All participants | 482/2104 (22.9) | 1110/4321 (25.7) | 0.83 (0.75-0.93) | 0.87 (0.78-0.97) |

* Main analysis shown in Figures 2 and 3, in which the 28-day age-adjusted (ie, conditional) mortality rate ratio is estimated by the hazard ratio from a Cox regression analysis adjusted for age in three categories (<70 years, 70-79 years, and ≥80 years or older). There was a clear trend towards greater benefit among patients requiring higher levels of respiratory support (chi-squared trend statistic = 15.1).

† One pre-specified analysis without adjustment for the 1.1-year age-imbalance between the randomized groups. With this method the 'one-step' method is used to estimate the average unadjusted (ie, marginal) mortality rate ratio from the log-rank 'observed minus expected' statistic (O-E) and its variance (V), through the formula $\exp(O-E)/V$. Its 95% CI is then given by $\exp(O-E) \pm 1.96 \cdot \sqrt{V}$. There was a clear trend towards greater benefit among patients requiring higher levels of respiratory support (chi-squared trend statistic = 15.1).

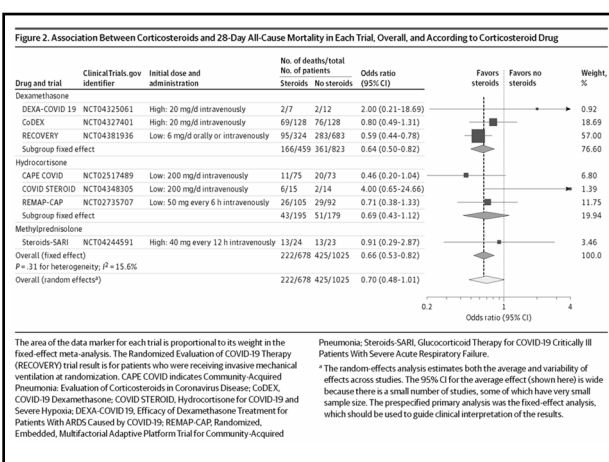
Relativ riskreduktion (RRR)=1-0.71=0.29=29%
 Absolut riskreduktion (ARR)=41.4%-29.3%=12.1%=0.121
 NNT=1/ARR=1/0.121=8.3

Metaanalys

Research
 JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT
Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19
 A Meta-analysis
 The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group
 JAMA. 2020; 324:1330-1341

Resultat från flera studier vägs samman, större studier väger tyngre för beräkning av effektstorlek.

I² (mått på heterogenitet): hur stor del av resultat-skillnader mellan studier som inte kan förklaras av slumpen. Vid I² > 50-75% anses metaanalys olämpligt.



The area of the data marker for each trial is proportional to its weight in the fixed-effect meta-analysis. The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial result is for patients who were receiving invasive mechanical ventilation at randomization. CAPE COVID indicates Community-Acquired Pneumonia: Evaluation of Corticosteroids in Coronavirus Disease. CoDEX COVID-19 Dexamethasone. COVID STEROID, Hydrocortisone for COVID-19 and Severe Hypoxia; DEXA-COVID 19, Efficacy of Dexamethasone Treatment for Patients With ARDS Caused by COVID-19; REMAP-CAP, Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia; Steroids-SARI, Glucocorticoid Therapy for COVID-19 Critically Ill Patients With Severe Acute Respiratory Failure. * The random effects analysis estimates both the average and variability of effects across studies. The 95% CI for the average effect (shown here) is wide because there is a small number of studies, some of which have very small sample sizes. The prespecified primary analysis was the fixed-effect analysis, which should be used to guide clinical interpretation of the results.

Odds och risk

| Behandling | Utfall | | Totalt |
|------------|--------|---------|--------|
| | Död | Levande | |
| a | b | a+b | |
| c | d | c+d | |

Risk (behandling) = a/a+b
 Risk (kontroll) = c/c+d
 Risk ratio (relativ risk) = (a/a+b)/(c/c+d)
 Odds (behandling) = a/b
 Odds (kontroll) = c/d
 Odds ratio (oddskvot) = (a/b)/(c/d)
 Vid låg risk (1/100) är den ca samma som odds (1/99).
 Vid hög risk (2/3 = 0.67) är odds mycket högre (2/1 = 2).

Odds och risk

Resultat från RECOVERY-studien:

| | Död | Levande | Totalt | Risk att dö | Odds för död |
|---------------------------|-----|---------|--------|-------------|--------------|
| Dexametason | 95 | 229 | 324 | 0.293 | 0.415 |
| Kontroll | 283 | 400 | 683 | 0.414 | 0.708 |
| Risk ratio (relativ risk) | | | | 0.708 | |
| Odds ratio | | | | | 0.586 |

I studien rapporterade man:

Rate ratio: 0.64 (95%CI 0.51-0.81, Cox Prop. Hazard)

Rate ratio: 0.67 (95%CI 0.54-0.84, log-rank test)

Här beräknade vi:

Risk ratio: 0.71 (95%CI 0.58-0.86)

I metaanalysen rapporteras:

Odds ratio: 0.59 (95%CI 0.44-0.78)

Odds och risk

Beräkning av 95%CI för odds ratio (OR):

OR ej normalfördelat men $\ln OR$ är.

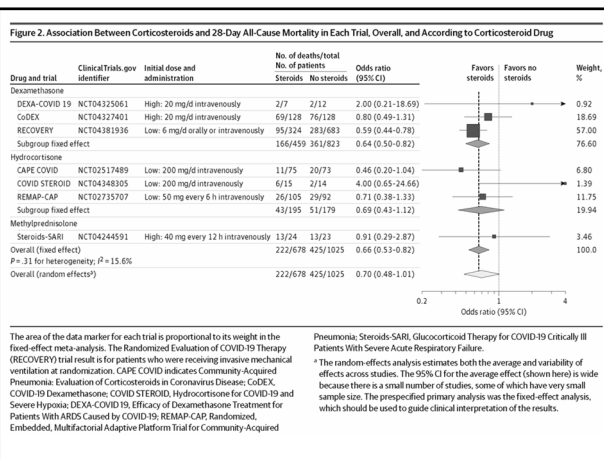
Standard error (se) för $\ln OR$ är $\sqrt{(1/a+1/b+1/c+1/d)}$

Beräkna $\ln OR + 1.96se$ och $\ln OR - 1.96se$ och återtransformera (e^x).

Beräkning av 95%CI för relativ risk (RR):

Gör på samma sätt men se för $\ln RR$ är

$\sqrt{(1/a-1/(a+b)+1/c-1/(c+d))}$



Metaanalys

Sammantaget resultat (odds ratio, OR):

Fixed effect model: OR 0.66 (95%CI 0.53-0.82)

Random effects model: OR 0.70 (95%CI 0.48-1.01)

Fixed effect model: Utgår från att det finns en "sann" effekt som är lika stor i alla ingående studier.

Random effects model: Utgår från att det finns en "sann" effekt i varje studie men att denna kan variera mellan studierna.

"The prespecified primary analysis was the fixed-effect analysis, which should be used to guide clinical interpretation of the results".