Obesity is a Risk Factor for Developing Critical Condition in COVID-19 Patients: A Systematic Review and Meta-analysis

Mária Földi1,2,3 foldimarcsi4@gmail.com, Nelli Farkas1,2 farkas.nelli@gmail.com, Szabolcs Kiss1,2,3 kissszabolcs1995@gmail.com, Noémi Zádori1,2 znoeemi@gmail.com, Szilárd Vánacs1,2 vancsaszilard@gmail.com, Lajos Szakó1,2 szklaj@gmail.com, Fanni Dembrovszky1,2 dembrovszky.f@gmail.com, Margit Solymár1,2 margit.solymar@aok.pte.hu, Eszter Bartalis1,4 19bortaliseszter95@gmail.com, Zsolt Szakács1,2 szaki92@gmail.com, Petra Hartmann5 drhartmann.petra@gmail.com, Gabriella Pár5 par.gabriella@pte.hu, Bálint Erőss1,2 eross.balint@pte.hu, Zsolt Molnár1,2,7 zsoltmolna@gmail.com, Péter Hegyi1,2 hegyi2009@gmail.com, and Andrea Szentesi1,2,8* szentesiai@gmail.com

1Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary; 2Szentágothai Research Centre, University of Pécs, Pécs, Hungary 3Doctoral School of Clinical Medicine, University of Szeged, Szeged, Hungary 4University of Medicine, Pharmacy, Science and Technology of Targu Mures, Targu Mures, Romania; (EB) 5Institute of Surgical Research, University of Szeged, Szeged, Hungary; 6Division of Gastroenterology, First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary 7Department of Anesthesiology and Intensive Therapy, Poznan University for Medical Sciences, Poznan, Poland 8First Department of Medicine, University of Szeged, Szeged, Hungary

*Correspondence: Andrea Szentesi, Operative Director

Address: Center for Translational Medicine, University of Pécs 12 Szigeti street, H-7624 Pécs, Hungary, Tel.: +36 30 342 1481, E-mail: szentesiai@gmail.com; Phone: +36-30-342-1481
### Study name | Statistics for each study | IMV / Total | Odds ratio and 95% CI | Relative weight
--- | --- | --- | --- | ---
Bhatraju, P, 2020 | Odds ratio 2.000 Lower limit 0.143 Upper limit 27.990 p-Value 0.607 Overweight and obesity 16 / 20 Normal weight 2 / 3 | | 3.19
Caussy, C, 2020 | Odds ratio 2.472 Lower limit 1.442 Upper limit 4.236 p-Value 0.001 Overweight and obesity 139 / 217 Normal weight 31 / 74 | | 76.63
Simonnet, A, 2020 | Odds ratio 3.505 Lower limit 1.227 Upper limit 10.014 p-Value 0.019 Overweight and obesity 81 / 107 Normal weight 8 / 17 | | 20.17
Overall | Odds ratio 2.634 Lower limit 1.644 Upper limit 4.221 p-Value 0.000 Overweight and obesity 236 / 344 Normal weight 41 / 94 | | 0.01 0.1 1 10 100

**Figure S1:** Forest plot comparing patients with overweight or obesity to patients with normal weight regarding invasive mechanical ventilation. IMV=invasive mechanical ventilation, CI=confidence interval
Figure S2: Meta-regression assessing the correlation between the body mass index and invasive mechanical ventilation, BMI=body mass index
Figure S3: Funnel plot assessing the publication bias of the meta-analysis that compares non-obese and obese patients regarding intensive care unit.
Figure S4: Funnel plot assessing the publication bias of the meta-analysis that compares non-obese and obese regarding invasive mechanical ventilation.
Table S1

| Section/topic        | #  | Checklist item                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Reported on page # |
|----------------------|----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| **TITLE**            |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                   |
| Title                | 1  | Identify the report as a systematic review, meta-analysis, or both.                                                                                                                                                                                                                                                                                                                                                           | 1/14              |
| **ABSTRACT**         |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                   |
| Structured summary   | 2  | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.                                                                                   | 1/14              |
| **INTRODUCTION**     |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                   |
| Rationale            | 3  | Describe the rationale for the review in the context of what is already known.                                                                                                                                                                                                                                                                                                                                        | 2/14              |
| Objectives           | 4  | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).                                                                                                                                                                                                          | 2/14              |
| **METHODS**          |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                   |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.                                                                                                                                                                                                                                         | 2/14              |
| Eligibility criteria | 6  | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.                                                                                                                                                                                                                                         | 2–3/14            |
| Information sources  | 7  | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.                                                                                                                                                                                                                                              | 2/14              |
| Search               | 8  | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                                                                                                                                                                                                                                                  | 2/14              |
| Study selection      | 9  | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                                                                                                                                                                                      | 2–3/14            |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.                                                                                                                                                                                                                                          | 3/14              |
| Data items           | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.                                                                                                                                                                                                                                                                                      | 3/14              |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.                                                                                                                                                                                                                     | 3/14              |
| Summary measures     | 13 | State the principal summary measures (e.g., risk ratio, difference in means).                                                                                                                                                                                                                                                                                                                                         | 2/14              |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis.                                                                                                                                                                                                            | 3/14              |
| Section/topic                        | #  | Checklist item                                                                                                                                                                                                 | Reported on page # |
|-------------------------------------|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| **Risk of bias across studies**     | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).                                                                          | NA                |
| **Additional analyses**             | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.                                                                       | 3/14              |
| **RESULTS**                         |    |                                                                                                                                                                                                                  |                   |
| **Study selection**                 | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.                                                    | 4/14              |
| **Study characteristics**           | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.                                                                     | 4–5/14            |
| **Risk of bias within studies**     | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).                                                                                                       | (8/14) + Table S5 |
| **Results of individual studies**   | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 6–8/14 + Figure S1, Table S3–4 |
| **Synthesis of results**            | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.                                                                                                         | 6–8/14            |
| **Risk of bias across studies**     | 22 | Present results of any assessment of risk of bias across studies (see Item 15).                                                                                                                                  | NA                |
| **Additional analysis**             | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).                                                                                             | 6-8/14            |
| **DISCUSSION**                      |    |                                                                                                                                                                                                                  |                   |
| **Summary of evidence**             | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).                                       | 8–9/14            |
| **Limitations**                     | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).                                                        | 9/14              |
| **Conclusions**                     | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.                                                                                           | 10/14             |
| **FUNDING**                         |    |                                                                                                                                                                                                                  |                   |
| **Funding**                         | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.                                                                       | 10/14             |

*From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097*

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org)
Table S2. Eligibility criteria in each included study in the meta-analysis

| Study                  | Outcome     | Definition                                                                                                                                                                                                 | Follow-up | Eligibility                                                                                                                                                                                                 |
|------------------------|-------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bhatraju PK et al      | IMV need    | Acute respiratory distress syndrome (ARDS) was defined as acute-onset hypoxemia (the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen [Pao2:Fio2], <300) with bilateral pulmonary opacities on chest imaging that were not fully explained by congestive heart failure or other forms of volume overload. | 23/03/2020| A confirmed case of Covid-19 was defined by a positive result on a reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of a specimen collected on a nasopharyngeal swab. Only laboratory-confirmed cases were included. Pregnant women, prisoners, and children (those younger than 18 years of age) were excluded from the study. |
| Caussy C et al         | IMV need    | Although we agree that invasive mechanical ventilation (IMV) can be considered as a reliable outcome for the severity of SARS-CoV-2, there is currently no guideline for the indication of IMV in the context of SRAS-CoV-2. | ND        | NR                                                                                                                                                                                                       |
| Hu L et al             | ICU admission | Based on the clinical presentation at the time of admission, patients were categorized into one of three groups: non-severe, severe and critical. | 10/03/2020| Diagnosis complied with the WHO interim guidance and the guidelines of COVID-19 diagnosis and treatment trial (5th edition), by the National Health Commission of the People’s Republic of China. |
| Itelman E et al        | ICU admission | We chose a simplified version to classify symptoms: mild disease included flu-like without clinical and imaging signs of pneumonia; moderate included pneumonia and hypoxemia; and severe included requiring intensive help for proper oxygenation (either high-flow oxygen delivery device or artificial ventilation, either non-invasive or invasive). | NR        | NR                                                                                                                                                                                                       |
| Kalligeros M et al     | ICU admission; ICU admission within the first 10 days of hospital admission with COVID-19. Our |                                                                                                                                          | NR        | consecutive adult (≥ 18 years old) patients, who had a laboratory confirmed (using a reverse                                                                                                                                 |


| Authors         | IMV need | Secondary objective was to assess if the aforementioned factors are associated with the need for IMV during the first 10 days of hospital admission with COVID-19. | transcriptase–polymerase chain reaction assay) SARS-Cov-2 infection |
|-----------------|----------|-------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|
| Lighter J et al | ICU admission | Critical care was defined based on intensive care accommodation status or invasive ventilator documentation in our electronic health record. | NR                                                                 | Patients who were PCR-positive for Covid-19                           |
| Lodigiani C et al | ICU admission | Patients requiring intensive care | NR | laboratory-proven COVID-19 |
| Ong S et al     | ICU admission IMV need | adverse outcomes analyzed were hypoxia requiring supplemental oxygen, ICU admission, mechanical ventilation, and mortality. | NR | laboratory confirmed COVID-19 (by polymerase chain reaction assay) |
| Peng YD et al   | ICU admission | Critical (one of the following situations): respiratory failure requires mechanical ventilation; shock; combined with other organ failure requires intensive care unit (ICU) | NR | patients with combined cardiovascular diseases (hypertension, coronary heart disease and heart failure) |
| Simonnet A et al | IMV need | The primary outcome of this study was the prevalence of patients receiving invasive mechanical ventilation (IMV) following admission to intensive care. The use of IMV was determined when oxygen therapy (≥ 10 L/min) with target spO2 (90-94%) was ineffective, and when respiratory rate was above 25/min, with signs of acute respiratory failure, despite maximal oxygen therapy. | 06/04/2020 | All patients were diagnosed with COVID-19 pneumonia according to World Health Organization interim guidance (11) with SARS symptoms characterized by dyspnea, increased respiratory frequency, decreased blood oxygen saturation, and need for oxygen support therapy for at least 6 L/min. Throat swab samples were obtained from all patients at admission and tested using real-time reverse transcriptase-polymerase chain reaction |
| Study name       | Study design | Country     | Event     | N0 of ALL patients | N0 of ALL patients with EVENT | BMI in the study |
|------------------|--------------|-------------|-----------|--------------------|------------------------------|------------------|
|                  |              |             |           |                    |                              | Mean  | SD  | Median | Range min | Range max | IQR min | IQR max |
| Alattar, R, 2020 | RC           | Qatar       | IMV       | 25                 | 21                           | 29    | 27  | 34     |
| Bessiére, F, 2020| RC           | France      | IMV       | 40                 | 30                           | 28    | 25  | 33     |
| Bhatraju, P, 2020| RC           | USA         | IMV       | 23                 | 18                           | 33.2  | 7.2 |        |
| Cardoso, FS, 2020| RC           | Portugal    | IMV       | 20                 | 20                           | 29    |     |        |
| Middeldrop, S, 2020| RC       | Netherlands | IMV       | 75                 | 75                           | 27    | 24  | 31     |
| Piva, S, 2020    | RC           | Italy       | IMV       | 33                 | 20                           | 27.8  |    |        |
| Poissy, J, 2020  | RC           | France      | IMV       | 22                 | 17                           | 30    | 22  | 53     |
| Simonnet, 2020   | RC           | France      | IMV       | 124                | 85                           | 29.6  |    |        |
| Spiezia, 2020    | RC           | Italy       | IMV       | 22                 | 19                           | 30    |     | 6      |
| Cai, Q, Huang, D, 2020| RC   | China       | ICU       | 298                | 34                           | 23.05 |      |        |
| Fang, Z, 2020    | RC           | China       | ICU       | 32                 | 8                            | 24.5  |    |        |
| Huang, R, Zhu, R | RC           | China       | ICU       | 202                | 11                           | 24.4  |    |        |
| Ji, D, Qin, E    | RC           | China       | ICU       | 202                | 1                            | 24    |     | 2.8    |
| Li, X, 2020      | RC           | China       | ICU       | 548                | 46                           | 24.7  |    |        |
| Peng, Y, 2020    | RC           | China       | ICU       | 112                | 17                           | 22    |     | 20     |
| Wu, J, 2020      | RC           | China       | ICU       | 280                | 83                           | 24.1  | 3   |        |
| Haberman, R, 2020| RC           | USA         | ICU       | 14                 | 1                            | 30.8  | 8   |        |
| Itelman, E, 2020 | RC           | Israel      | ICU       | 162                | 26                           | 27.3  |    | 23.9   |
| Mercuno, NJ, 2020| RC           | Israel      | ICU       | 90                 | 30                           | 31.5  | 6.6 |        |
| Middeldrop, S, 2020| RC   | Netherlands | ICU       | 198                | 75                           | 27    |     |        |

Abbreviations: RC=retrospective, BMI=body mass index, IMV=invasive mechanical ventilation, ICU=intensive care unit, SD=standard deviation, IQR=interquartile range
Table S4. Study-level data on multivariate analysis

| Study name (country) | Investigated event | Risk factor (reference: BMI<25) | Adjusted factors in multivariate logistic regression | OR (95% CI) | p value |
|----------------------|---------------------|---------------------------------|-----------------------------------------------------|-------------|---------|
| Kalligeros et al. (USA) (103 patients in the study) | ICU admission | BMI 25-29.9 | age, race, gender | 2.14 (0.58-7.88) | 0.25 |
| Kalligeros et al. (USA) | ICU admission | BMI 25-29.9 | age, race, gender, diabetes, hypertension, lung disease¹, heart disease² | 2.27 (0.59-8.83) | 0.235 |
| Kalligeros et al. (USA) | ICU admission | BMI 30-34.9 | age, race, gender | 2.56 (0.64-10.1) | 0.1 |
| Kalligeros et al. (USA) | ICU admission | BMI 30-34.9 | age, race, gender, diabetes, hypertension, lung disease¹, heart disease² | 2.65 (0.64-10.95) | 0.178 |
| Kalligeros et al. (USA) | ICU admission | BMI≥35 | age, race, gender | **6.16 (1.42-26.66)** | **0.015** |
| Kalligeros et al. (USA) | ICU admission | BMI≥35 | age, race, gender, diabetes, hypertension, lung disease¹, heart disease² | **5.39 (1.13-25.64)** | **0.034** |
| Kalligeros et al. (USA) (34 patients in the study) | IMV | BMI 25-29.9 | age, race, gender | 2.64 (0.48-14.4) | 0.262 |
| Kalligeros et al. (USA) | IMV | BMI 25-29.9 | age, race, gender, diabetes, hypertension, lung disease¹, heart disease² | 3.70 (0.60-22.87) | 0.159 |
| Kalligeros et al. (USA) | IMV | BMI 30-34.9 | age, race, gender | 5.28 (0.91-30.48) | 0.063 |
| Kalligeros et al. (USA) | IMV | BMI 30-34.9 | age, race, gender, diabetes, hypertension, lung disease¹, heart disease² | **6.85 (1.05-44.82)** | **0.045** |
| Study                                      | Treatment | BMI Range | Other Factors                        | Odds Ratio (95% CI) | p-value |
|--------------------------------------------|-----------|-----------|--------------------------------------|---------------------|---------|
| Kalligeros et al. (USA)                    | IMV       | BMI ≥35   | age, race, gender                    | 8.19 (1.36-49.13)   | 0.021   |
|                                            |           |           | age, race, gender, diabetes, hypertension, lung disease¹, heart disease² | 9.99 (1.39-71.69)   | 0.022   |
| Simonnet et al. (France)                   | IMV       | BMI 25-30.0 | age, diabetes, hypertension          | 1.69 (0.52-5.48)    | 0.22    |
| (124 patients in the study)                |           |           | age, diabetes, hypertension          | 3.45 (0.83-12.31)   | 0.48    |
| Simonnet et al. (France)                   | IMV       | BMI 30-35 | age, diabetes, hypertension          | 7.36 (1.63-33.14)   | 0.021   |

¹: COPD, asthma, interstitial lung disease and pulmonary hypertension; ²: heart failure, coronary artery disease and cardiomyopathy

Abbreviations: IMV = invasive mechanical ventilation, ICU = intensive care unit, BMI = body mass index, CI = confidence interval
### Table S5. Risk of bias assessment with QUIPS tool

| Study | Study participation | Study attrition | Obesity | Mechanical ventilation | Intensive care unit adm. | Study confounding | Statistical analysis reporting |
|-------|---------------------|-----------------|---------|-------------------------|--------------------------|-------------------|-----------------------------|
| Alattar R, Ibrahim T | ✔ | N/A | ✔ | ? | ? | ? | ✔ |
| Bessiere F, Roccia H | ✔ | N/A | ✔ | ? | ? | ? | ✔ |
| Bhataju PK, Ghassemieh BJ | ✔ | N/A | ✔ | ? | ? | ? | ✔ |
| Cai Q, Huang D | ✔ | N/A | ✔ | ? | ? | ? | ✔ |
| Cardoso FS, Pereira R | ? | N/A | ✔ | ? | ? | ? | ✔ |
| Caussy C, Wallet F | ? | N/A | ✔ | ? | ? | ? | ✔ |
| Fang Z, Zhang Y | ✔ | N/A | ✔ | ? | ? | N/A | ? |
| Haberman R, Axelrad J | ✫ | ? | ✫ | ? | ✫ | ? | ✫ |
| Hu L, Chen S | ✔ | N/A | ✔ | ? | N/A | ✫ | ✫ |
| Huang R, Zhu Li | ✔ | N/A | ✔ | ? | ? | ? | ✫ |
| Itelman E, Waaserstrum Y | ? | N/A | ✫ | ? | ? | ? | ✫ |
| Ji D, Qin E | ✔ | ? | ✔ | ? | ? | ? | ✫ |
| Kalligeros M, Shehadeh F | ✔ | N/A | ✫ | ? | ? | ? | ✫ |
| Li X, Xu S | ✔ | ✫ | ✫ | ? | N/A | ? | ✫ |
| Lighter J, Phillips M | ✔ | N/A | ✔ | ? | ✫ | ? | ✫ |
| Lodigiani C, Lapichino G | ✫ | N/A | ✔ | ? | ? | ? | ✫ |
| Mercuro NJ, Yen CF | ✫ | N/A | ✫ | ? | ✫ | ? | ✫ |
| Middeldorp S, Coppens M | ✫ | N/A | ✫ | ? | ? | ? | ✫ |
| Ong S, Young BE | ✫ | N/A | ✫ | ? | ? | ? | ✫ |
| Peng YD, Meng K | ✫ | N/A | ✫ | ? | ? | ? | ✫ |
| Piva S, Filippini M | ✫ | ? | ✫ | ✫ | N/A | ? | ✫ |
| Poissy J, Goutay J | ? | N/A | ✫ | ? | N/A | ? | ✫ |
| Simonet A, Chetboun M | ✫ | N/A | ✫ | ? | N/A | ? | ✫ |
| Spieza L, Boscolo A | ? | N/A | ✫ | N/A | ? | ? | ✫ |
| Wu J, Li W | ✫ | N/A | ✫ | ? | ? | ? | ✫ |

Results of the modified QUIPS tool. By study participation the article was considered as carrying low risk of bias, if the diagnosis of COVID-19 was clearly stated, unclear risk of bias was given in the case of lacking description and high risk of bias was assessed if suspected or unclear cases were also involved. Study attrition was only assessed in the cases of prospective studies, where green indicates the clear description of follow-up, while yellow means a lacking description. Obesity as the only investigated prognostic factor was considered carrying low risk of bias on individual study level if BMI was assessed. A clear description of the outcomes was needed to achieve low risk of bias. In the case of confounding factors, green indicates a multivariate analysis, yellow means a lacking description and red is associated with the presence of a major confounding factor (e.g. age, gender, treatment etc.). As none of the studies has previously published protocol with statistical plan, we waived the need for the assessment of the statistical analysis reporting.

- **High risk**
- **Unclear risk**
- **Low risk**