Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

The association of dementia with COVID-19 mortality: Evidence based on adjusted effect estimates

Patients with dementia may be particularly vulnerable in the ongoing coronavirus disease 2019 (COVID-19) pandemic. Recently, Canevelli et al. reported that the prevalence of dementia among 2621 COVID-19-related deaths in Italy was 15.8%, which is significantly higher than expected based on the considered reference data (15.8% vs. 11.3%, $P < 0.001$). The authors concluded that dementia conferred a relevant risk of adverse outcomes among COVID-19 patients.[1] To our knowledge, there are several published papers investigating the association between dementia and the risk of mortality among COVID-19 patients, but the conclusions are not consistent, for example, the significant association between dementia and the risk of mortality among COVID-19 patients was reported in Berenguer et al.'s study[2] and Elmunzer et al.' study,[3] but other studies did not observe the significant association of dementia with the risk of mortality among COVID-19 patients.[4–6] Therefore, there is an urgent need to address the association of dementia with COVID-19 mortality by a quantitative meta-analysis. It has been reported that some risk factors including age, gender and co-existing diseases had obvious effects on disease outcomes of COVID-19 patients.[7–10] This suggests that these risk factors might affect the association between dementia and COVID-19 mortality. Therefore, our present meta-analysis was performed on the basis of multiple risk factors-adjusted effect estimates rather than unadjusted effect estimates.

This meta-analysis was conducted in the light of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. We performed a systematic literature search in online databases including PubMed, EMBASE and Web of Science to identify potentially eligible studies dated from January 1, 2020 to February 1, 2021. Keywords were used: "COVID-19", "SARS-CoV-2", "coronavirus disease 2019" and "dementia". The clinical outcome was defined as mortality (death, fatality, mortality, non-survivor, deceased or died). Studies were included in this meta-analysis if they reported the association between dementia and COVID-19 mortality estimated by using multivariable analysis model. Non-English papers, non-peer-reviewed papers, duplicated papers, case reports, comments, errata, protocols, review papers, articles reporting other clinical outcomes (such as severe, critical, severity, intensive care unit admission, mechanical ventilation, intubation, adverse outcomes, or composite outcomes) and articles with insufficient information were excluded. Two authors (Haiyan Yang and Xuan Liang) independently extracted data from each eligible study. The general information extracted included: author name, age, gender distribution, country/region, study design, sample size, adjusted risk factors, adjusted effect estimates, and clinical outcomes. Questions or disagreements were resolved by discussing with a third author (Yadong Wang).

The pooled effects along with 95% confidence interval (CI) were calculated by a random-effects model to estimate the association between dementia and the risk of COVID-19 mortality. The I^2 statistic was used to evaluate the heterogeneity across studies. Publication bias was assessed by the Egger's linear regression test. Stability of the results was assessed by sensitivity analysis. The statistical significance was defined as $P < 0.05$. All data analyses were conducted by Stata 12.1 software.

Initially, 1928 articles were identified through literature search. After detailed assessment according to inclusion and exclusion criteria, we included 34 studies with 182,280 confirmed COVID-19 patients reporting the association between dementia and COVID-19 mortality estimated by multivariable analysis. Among the 34 included studies, there are 18 studies from Europe (seven from UK, five from Spain, four from Italy, and one each from Denmark and the Netherlands, respectively), nine from North America (eight from USA and one from USA and Canada, respectively), six from Asia (four from Korea and two from Turkey, respectively), and the last one from international multicenter. The sample size across the eligible studies ranged from 69 to 35,302. The main characteristics of the included studies are shown in Table 1.

In total, we observed that COVID-19 patients with dementia had a significantly increased risk for mortality compared to those without dementia (pooled effect estimate = 1.84, 95% CI: 1.57–2.16, Fig. 1A) based on 34 eligible studies reporting adjusted effect estimates. Consistent results were observed in the further subgroup analyses stratified by region (pooled effect estimate = 1.86, 95% CI: 1.48–2.34 among Europe, pooled effect estimate = 1.49, 95% CI: 1.27–1.75 among North America, and pooled effect estimate = 2.83, 95% CI: 1.59–5.02 among Asia), age (pooled effect estimate = 1.85, 95% CI: 1.43–2.39 for ≥ 65 years and pooled effect estimate = 1.70, 95% CI: 1.46–1.97 for < 65 years), sample size (pooled effect estimate = 1.86, 95% CI: 1.52–2.27 for ≥ 1500 cases and pooled effect estimate = 1.83, 95% CI: 1.38–2.41 for < 1500 cases), proportion of male (pooled effect estimate = 2.04, 95% CI: 1.59–2.63 for ≥ 50% and pooled effect estimate = 1.61, 95% CI: 1.36–1.91 for < 50%), study design (pooled effect estimate = 1.58, 95% CI: 1.39–1.79 for retrospective study, pooled effect estimate = 1.83, 95% CI: 1.06–3.17 for prospective study, and pooled effect estimate = 3.06, 95% CI: 2.15–4.36 for others), effect estimates (hazard ratio (HR) = 1.79, 95% CI: 1.28–2.49, odds ratio (OR) = 1.82, 95% CI: 1.55–2.12, and relative risk (RR) = 2.11, 95% CI: 1.50–2.96). Sensitivity analysis by omitting each eligible study one by one demonstrated that our findings were stable and robust (Fig. 1B). Egger's test indicated that no publication bias existed in this current meta-analysis ($P = 0.893$).

Several limitations exist in this meta-analysis. Firstly, the included studies are mainly retrospective, only three are prospective. Thus, further well-designed studies with more prospective studies are required to verify our findings. Secondly, although the in-

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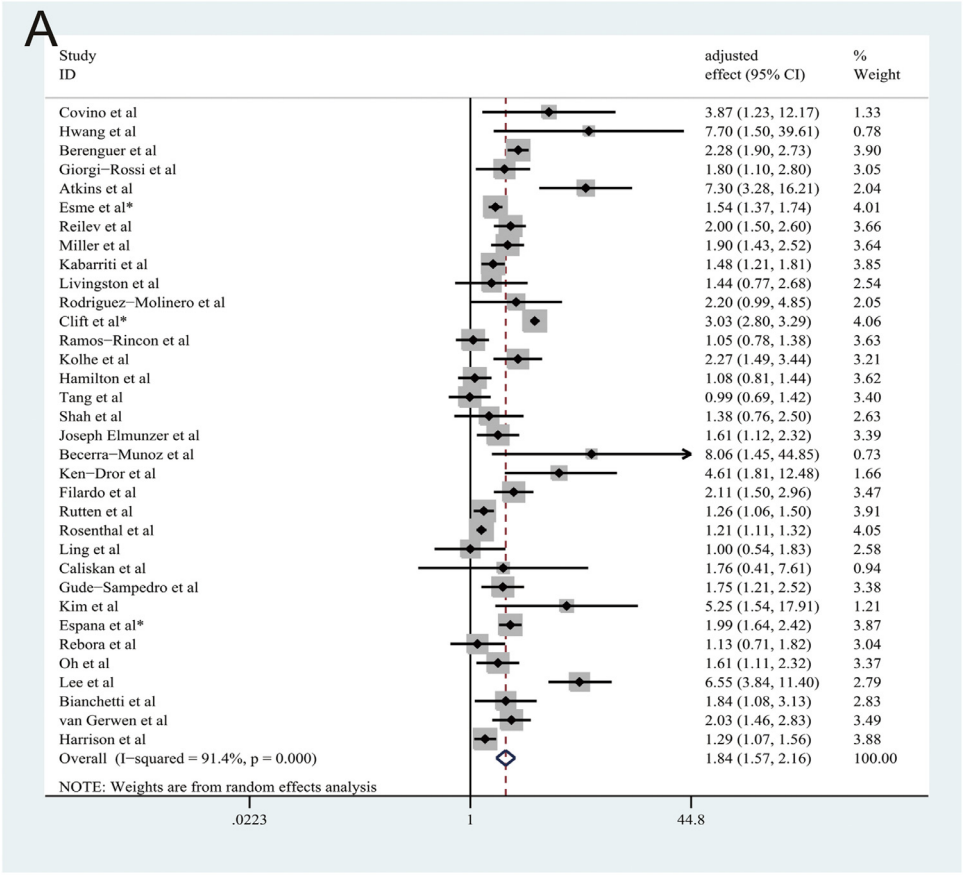

Fig. 1. (A) The forest plot demonstrating the pooled effect estimate and 95% confidence interval (CI) on the association between co-existing dementia and the risk of mortality among coronavirus disease 2019 (COVID-19) patients; (B) Leave-one-out sensitivity analysis was performed to evaluate the stability of results. * indicates that the combined values were calculated on the basis of data from subgroups.

cluded studies reported the adjusted effect estimates, the adjusted risk factors are not entirely consistent across the included studies. Thirdly, the included studies are mainly from Europe. The findings should be confirmed by future studies from other regions. Fourthly, heterogeneity between studies is obvious, but subgroup analyses and sensitivity analysis proved that our findings were stable and robust.

In conclusion, our study demonstrated that co-existing dementia was independently associated with a significantly increased risk of mortality among COVID-19 patients. Thus, special preventive

Table 1
Main characteristics of the studies included in this meta-analysis.

First author	Region	No. of cases	Proportion of male (%)	Age (years)	Study design	Adjusted-effect (95% CI)	Adjusted risk factors	Outcome
Covino et al. (PMID: 32,516,861)	Italy	69	53.6	84 (82–89)	Retrospective study	HR = 3.87 (1.23–12.17)	Peripheral oxygen saturation, blood urea nitrogen, lactate dehydrogenase, C-reactive protein	Death
Hwang et al. (PMID: 32,643,133)	Korea	103	50	67.62 ± 15.32	Retrospective study	HR = 7.698 (1.496–39.610)	Age, diabetes mellitus, chronic lung disease, cardiovascular disease, stroke	Death
Atkins et al. (PMID: 32,687,551)	UK	507	61.3	74.3 ± 4.5	Community-based study	OR = 7.30 (3.28–16.21)	Age group, sex, ethnicity, education, baseline assessment center, coronary heart disease, atrial fibrillation, stroke, hypertension, diabetes (type 2), chronic kidney disease, depression, asthma, chronic obstructive pulmonary disease, osteoporosis, osteoarthritis	Death
Berenguer et al. (PMID: 32,758,659)	Spain	3979	61	70 (56–80)	Retrospective study	HR = 2.28 (1.90–2.73)	Sex, age, arterial hypertension, obesity, liver cirrhosis, chronic neurological disorder, active cancer, dyspnea, confusion, low age-adjusted SaO_2 on room air, higher white cell blood count, higher neutrophil-to-lymphocyte ratio, lower platelet count, international normalized ratio, estimated glomerular filtration rate, concentrations of C-reactive protein	Death
Giorgi-Rossi et al. (PMID: 32,853,230)	Italy	2653	50.1	63.48 ± 23.82	Prospective study	HR = 1.8 (1.1–2.8)	Age, sex	Death
Esme et al. (PMID: 32,871,002)	Turkey	16,942	49	70.30 ± 9.71	Retrospective study	OR = 1.63 (1.36–1.94) OR = 1.47 (1.24–1.73)	Gender, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, coronary artery disease, atrial fibrillation, chronic kidney disease, depression, malnutrition, and hyperlipidemia	Mortality
Reilev et al. (PMID: 32,887,982)	Denmark	11,122	42.2	48 (33–62)	Population-based study	OR = 2.0 (1.5–2.6)	Age, sex	Death
Miller et al. (PMID: 32,945,856)	USA	3633	46.2	58.4 ± 18.1	Retrospective study	OR = 1.90 (1.43–2.52)	Demographic, socioeconomic, and comorbid condition data	Mortality
Kabarriti et al. (PMID: 32,975,574)	USA	5902	46.9	57.74 ± 21.60	Retrospective study	HR = 1.48 (1.21–1.81)	Sex, age, socioeconomic status, ethnicity, body mass index, hypertension, diabetes, cancer, liver disease, chronic pulmonary disease, peptic ulcer, hemiplegia or paraplegia, kidney disease, human immunodeficiency virus/acquired immunodeficiency syndrome	Death
Livingston et al. (PMID: 33,031,760)	UK	131	48.1	57.3 ± 8.2	Retrospective study	OR = 1.44 (0.77–2.68)	Number of comorbidities	Death
Rodriguez-Molinero et al. (PMID: 33,057,443)	Spain	418	56.9	65.4 ± 16.6	Observational study	OR = 2.20 (0.99–4.85)	Age, sex, diabetes mellitus, dyslipidemia, obesity, chronic kidney disease, hypertension, heart failure, atrial fibrillation, obstructive sleep apnea syndrome, auto-immune disease	Fatality
Clift et al. (PMID: 33,082,154)	UK	10,776	55.3	69.63 ± 17.90	Cohort study	HR = 2.91 (2.58–3.28) HR = 3.14 (2.81–3.50)	Age, body mass index, townsend score (linear), ethnic group, domicile (residential care, homeless, neither), and a range of conditions and treatments	Death
Ramos-Rincon et al. (PMID: 33,103,720)	Spain	2772	49.4	86.3 (83.2–89.6)	Retrospective study	OR = 1.05 (0.78–1.38)	Age, sex, comorbidities, symptoms, physical exam, laboratory findings	Mortality
Kolhe et al. (PMID: 33,125,416)	UK	1161	56.6	72.10 ± 16.01	Retrospective study	OR =2.27 (1.49–3.44)	Age, sex, ethnicity, myocardial infarction, congestive cardiac failure, peripheral vascular disease, cerebrovascular disease, chronic lung disease, connective tissue disorder, diabetes with complications, paraplegia, chronic kidney disease, chronic liver disease, cancer	Mortality
Hamilton et al. (PMID: 33,141,867)	UK	1032	55.1	71 (56–83)	Retrospective study	HR = 1.08 (0.81–1.44)	Acute kidney injury, cancer, ethnicity, diabetes, sex, mayocardial infarction, age, renin-angiotensin-aldosterone-system inhibitors	Death
Tang et al. (PMID: 33,153,910)	USA	752	39.9	71.16 ± 51.68	Retrospective study	HR= 0.99 (0.69–1.42)	Age, sex, race, facility	Mortality
Shah et al. (PMID: 33,169,090)	USA	487	56.1	68.42 ± 16.70	Retrospective study	OR = 1.38 (0.76–2.50)	Age, gender, patient admitted from home, hypertension, hyperlipidemia, cardiomyopathy, atrial fibrillation, chronic obstructive pulmonary disease, cerebrovascular accident, diabetes mellitus, acute kidney injury	Mortality

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Table 1 (*continued*)

First author	Region	No. of cases	Proportion of male (%)	Age (years)	Study design	Adjusted-effect (95% CI)	Adjusted risk factors	Outcome
Joseph Elmunzer et al. (PMID: 33,189,702)	USA and Canada	1846	56.6	59.9 ± 16.4	Retrospective study	OR = 1.61 (1.12–2.32)	Age, sex, race, PPI use, H2RA use, laboratory values at admission	Death
Becerra-Munoz et al. (PMID: 33,201,181)	International multicenter	1520	60.3	76 (71–83)	A comparetive study	OR = 8.06 (1.45–44.85)	Age, male, hypertension, diabetes, lung disease, cerebrovascular disease, any heart disease, chronic kidney disease, liver disease, parkinson disease, any dependency level, home oxygen therapy, premedication with angiotensin converting enzyme (ACE) inhibitors/angiotensin receptors blockers, dyspnea, peripheral oxygen saturation <92%, elevated D-dimer, elevated procalcitonin, elevated C-reactive protein, elevated troponin, elevated lactate dehydrogenase, severe lymphopenia (<500), quick sequential organ failure assessment score >1, in-hospital use of glucocorticoids, in-hospital use of chloroquine, in-hospital use of antiviral drugs	Mortality
Ken-Dror et al. (PMID: 33,199,428)	UK	429	56.4	70 ± 18	Prospective study	OR = 4.61 (1.81–12.48)	Age, C-reactive protein, respiratory rate, diastolic blood pressure, asthma, akaike information criterion, seneitivity/specificity, area under the curve	Mortality
Filardo et al. (PMID: 33,227,019)	USA	270	67.4	58 (50–67)	Retrospective study	RR = 2.11 (1.50–2.96)	Age, sex, race, cardiovascular comorbidities, pulmonary comorbidities, renal comorbidities, type 2 diabetes, immunosuppression, human immunodeficiency virus, malignancy, obesity	Mortality
Rutten et al. (PMID: 33,256,958)	The Netherlands	1538	36	84 ± 8.7	Prospective study	HR = 1.26 (1.06–1.50)	Gender, age, comorbidities	Mortality
Rosenthal et al. (PMID: 33,301,018)	USA	35,302	53.4	63.6 ± 17.7	Retrospective study	OR = 1.21 (1.11–1.32)	Age, sex, race, payer type, admission point of origin, hospital region, hospital beds, hospital teaching status, statin, vitamin C, zinc, angiotensin-converting enzyme inhibitor, b blocker, calcium channel blocker, hydroxychloroquine and azithromycin use, sepsis, acute kidney failure, hypokalemia, hyperkalemia, hyponatremia, acidosis, acute liver damage, neurological disorder, myocardial infarction, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, diabetes, any malignant neoplasm, metastatic solid tumor, hemiplegia, acquired immunodeficiency syndrome, hypertension	Mortality
Ling et al. (PMID: 33,322,317)	UK	444	55.2	74 (63–83)	Retrospective study	OR = 1.00 (0.54–1.83)	Age, sex, obesity, ethnicity, diabetes	Mortality
Caliskan et al. (PMID: 33,331,576)	Turkey	565	NR	48 ± 19.7	Retrospective study	OR = 1.762 (0.408–7.607)	Former smoker, current smoker, age, chronic obstructive pulmonary disease, diabetes, coronary artery disease, hypertension, congestive heart failure, arrhythmia	Mortality
Gude-Sampedro et al. (PMID: 33,349,845)	Spain	10,454	39.9	58.0 ± 20.0	Retrospective study	OR = 1.75 (1.21–2.52)	Age, gender and comorbidities	Death
Kim et al. (PMID: 33,398,946)	Korea	2254	35.8	58 (42.0–70.0)	Retrospective study	HR =5.252 (1.540–17.910)	Age, fever, need for O_2 supply at admission, diabetes, cancer, heart failure, hypertension, neurological disease, infiltration on chest X-ray at initial diagnosis, body mass index, chronic liver disease	Mortality
Espana et al. (PMID: 33,400,164)	Spain	18,768	61.5	59.54 ± 16.45	Retrospective study	OR = 1.80 (1.44–2.25) OR = 2.74 (1.84–4.10)	Gender, age, hospital admission, previous hospital admissions 1 month, cardiovascular, respiratory, liver disease, diabetes, kidney, cancer, basal treatment	Death
Rebora et al. (PMID: 33,411,332)	Italy	516	62	78 (73–84)	Retrospective study	HR = 1.13 (0.71–1.82)	Sex, age, delirium, functional disability, No. of chronic diseases, use of continuous positive airway pressure, nutritional status, chest X-ray or computed tomography, C-reactive protein	Mortality

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Table 1 (*continued*)

First author	Region	No. of cases	Proportion of male (%)	Age (years)	Study design	Adjusted-effect (95% CI)	Adjusted risk factors	Outcome
Oh et al. (PMID: 33,407,347)	Korea	7780	NR	NR	Population-based cohort study	OR = 1.61 (1.11–2.32)	Charlson comorbidity index, hypertension, diabetes mellitus, peripheral vascular disease, renal disease, rheumatic disease, peptic ulcer disease, hemiplegia or paraplegia, moderate or severe liver disease, mild liver disease, cerebrovascular disease, congestive heart failure, myocardial infarction, malignancy, metastatic solid tumor, acquired immune deficiency syndrome/human immunodeficiency virus	Death
Lee et al. (PMID: 33,530,509)	Korea	4052	38.7	NR	Longitudinal cohort study	OR = 6.55 (3.84–11.40)	Age, systolic blood pressure, heart rate, dyspnea at presentation, mental disturbance at presentation, diarrhea at presentation, treating cancer, diabetes, hypertension, chronic cardiac disease, chronic pulmonary disease, chronic renal disease, hemoglobin, absolute lymphocyte counts, platelet counts	Death
Bianchetti et al. (PMID: 32,510,106)	Italy	627	46.6	70.7 ± 12.9	Retrospective study	OR = 1.84 (1.08–3.13)	age, sex	Mortality
van Gerwen et al. (PMID: 32,706,392)	USA	2015	58.6	64.5 ± 16.4	Retrospective study	OR = 2.03 (1.46–2.83)	Age group, gender, race, body mass index, smoking status, and comorbidities (hypertension, coronary artery disease, atrial fibrillation, congestive heart failure, peripheral vascular disease, cerebrovascular accident/transient ischemic attack, diabetes, hypothyroidism, chronic kidney disease, malignancy, asthma, chronic obstructive pulmonary disease, prior venous thromboembolism)	Death
Harrison et al. (PMID: 32,911,500)	USA	31,461	45.5	50 (35–63)	Retrospective study	OR = 1.29 (1.07–1.56)	Age, sex, comorbidities	Mortality

Note: CI, confidence interval; NR, not clearly reported; OR, odds ratio, HR, hazard ratio; RR, relative risk; UK, United Kingdom; USA, the United States of America. The value of age (years) was presented as mean ± standard deviation (SD) or median (interquartile range, IQR).

measures should be taken to protect individuals with dementia from exposure to SARS-CoV-2 and more medical attention should be given to COVID-19 patients with co-existing dementia to prevent disease deterioration.

References

1. Canevelli M, Palmieri L, Raparelli V, Lo Noce C, Colaizzo E, Tiple D, et al. Prevalence and clinical correlates of dementia among COVID-19-related deaths in Italy. *Alzheimer's Dementia* 2020;**12**(1):e12114 PubMed PMID: 33225041. Pubmed Central PMCID: 7666428.
2. Berenguer J, Ryan P, Rodriguez-Bano J, Jarrin I, Carratala J, Pachon J, et al. Characteristics and predictors of death among 4035 consecutively hospitalized patients with COVID-19 in Spain. *Clin Microbiol Infect* 2020;**26**(11):1525–36 PubMed PMID: 32758659. Pubmed Central PMCID: 7399713.
3. Elmunzer BJ, Wolf BJ, Scheiman JM, Tierney WM, Taylor JR. North American Alliance for the Study of Digestive Manifestations of C. Association between pre-admission acid suppressive medication exposure and severity of illness in patients hospitalized with COVID-19. *Gastroenterology* 2020 PubMed PMID: 33189702. Pubmed Central PMCID: 7659802. doi:10.1053/j.gastro.2020.11.007.
4. Hamilton P, Hanumapura P, Castelino L, Henney R, Parker K, Kumar M, et al. Characteristics and outcomes of hospitalised patients with acute kidney injury and COVID-19. *PLoS One* 2020;**15**(11):e0241544 PubMed PMID: 33141867. Pubmed Central PMCID: 7608889.
5. Ramos-Rincon JM, Buonaiuto V, Ricci M, Martin-Carmona J, Paredes-Ruiz D, Calderon-Moreno M, et al. Clinical characteristics and risk factors for mortality in very old patients hospitalized with COVID-19 in Spain. *J Gerontol Ser A Biol Sciences and Med Sci* 2020 PubMed PMID: 33103720. doi:10.1093/gerona/glaa243.
6. Rodriguez-Molinero A, Galvez-Barron C, Minarro A, Macho O, Lopez GF, Robles MT, et al. Association between COVID-19 prognosis and disease presentation, comorbidities and chronic treatment of hospitalized patients. *PLoS One* 2020;**15**(10):e0239571 PubMed PMID: 33057443. Pubmed Central PMCID: 7561079.
7. Mesas AE, Cavero-Redondo I, Álvarez-Bueno C, Sarriá Cabrera MA, Maffei de Andrade S, Sequí-Dominguez I, et al. Predictors of in-hospital COVID-19 mortality: a comprehensive systematic review and meta-analysis exploring differences by age, sex and health conditions. *PLoS One* 2020;**15**(11):e0241742 PubMed PMID: 33141836. Pubmed Central PMCID: PMC7608886. Epub 2020/11/04. eng.
8. Nasiri MJ, Haddadi S, Tahvildari A, Farsi Y, Arbabi M, Hasanzadeh S, et al. COVID-19 clinical characteristics, and sex-specific risk of mortality: systematic review and meta-analysis. *Front Med* 2020;**7**:459 PubMed PMID: 32793620. Pubmed Central PMCID: PMC7385184. Epub 2020/08/15. eng.
9. Liang X, Shi L, Wang Y, Xiao W, Duan G, Yang H, et al. The association of hypertension with the severity and mortality of COVID-19 patients: evidence based on adjusted effect estimates. *J Infect* 2020;**81**(3):e44–ee7 PubMed PMID: 32593655. Pubmed Central PMCID: 7315979 conflicts of interest.
10. Yang H, Xu J, Liang X, Shi L, Wang Y. Autoimmune diseases are independently associated with COVID-19 severity: evidence based on adjusted effect estimates. *J Infect* 2020 PubMed PMID: 33383087. doi:10.1016/j.jinf.2020.12.025.

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