Mortality-related risk factors of COVID-19: a systematic review and meta-analysis of 42 studies and 423,117 patients

Zelalem G. Dessie1,2* and Temesgen Zewotir1

Abstract

Background: Mortality rates of coronavirus disease-2019 (COVID-19) continue to rise across the world. The impact of several risk factors on coronavirus mortality has been previously reported in several meta-analyses limited by small sample sizes. In this systematic review, we aimed to summarize available findings on the association between comorbidities, complications, smoking status, obesity, gender, age and D-dimer, and risk of mortality from COVID-19 using a large dataset from a number of studies.

Method: Electronic databases including Google Scholar, Cochrane Library, Web of Sciences (WOS), EMBASE, Medline/PubMed, COVID-19 Research Database, and Scopus, were systematically searched till 31 August 2020. We included all human studies regardless of language, publication date or region. Forty-two studies with a total of 423,117 patients met the inclusion criteria. To pool the estimate, a mixed-effect model was used. Moreover, publication bias and sensitivity analysis were evaluated.

Results: The findings of the included studies were consistent in stating the contribution of comorbidities, gender, age, smoking status, obesity, acute kidney injury, and D-dimer as a risk factor to increase the requirement for advanced medical care. The analysis results showed that the pooled prevalence of mortality among hospitalized patients with COVID-19 was 17.62% (95% CI 14.26–21.57%, 42 studies and 423,117 patients). Older age has shown increased risk of mortality due to coronavirus and the pooled odds ratio (pOR) and hazard ratio (pHR) were 2.61 (95% CI 1.75–3.47) and 1.31 (95% CI 1.11–1.51), respectively. A significant association were found between COVID-19 mortality and male (pOR = 1.45; 95% CI 1.41–1.51; pHR = 1.24; 95% CI 1.07–1.41), and current smoker (pOR = 1.42; 95% CI 1.01–1.83). Furthermore, risk of mortality among hospitalized COVID-19 patients is highly influenced by patients with Chronic Obstructive Pulmonary Disease (COPD), Cardiovascular Disease (CVD), diabetes, hypertension, obese, cancer, acute kidney injury and increase D-dimer.

Conclusion: Chronic comorbidities, complications, and demographic variables including acute kidney injury, COPD, diabetes, hypertension, CVD, cancer, increased D-dimer, male gender, older age, current smoker, and obesity are clinical risk factors for a fatal outcome associated with coronavirus. The findings could be used for disease’s future research, control and prevention.

Keywords: Comorbidities, Demographic characteristics, Funnel plot, Heterogeneity, Publication bias, Sensitivity analysis

*Correspondence: DessieZ@ukzn.ac.za
1 School of Mathematics, Statistics and Computer Science, University of KwaZulu-Natal, Durban, South Africa
Full list of author information is available at the end of the article
Introduction

The 2019 novel coronavirus (2019-nCoV) is a newly emerging disease that was first reported in China, and has subsequently spread worldwide. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which belong to the family of Betacoronavirus genus [1]. Although the clinical presentation and symptoms of COVID-19 are similar to that of Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS), the rate of spread is greater [2]. On 11 March 2019, the WHO defined COVID-19 as a pandemic disease [3], and as of February 2021, a total of 107,496,792 cases and 2,353,308 deaths (3.0%) have been confirmed worldwide in 219 countries [4]. It is a major challenge for many countries to identify what measures could be used to avoid death or severe illness.

The challenge of COVID-19 is very high globally due to the complexity of its transmission and a lack of proven treatment [5, 6]. It will be more disastrous for middle and low-income countries because of their high illiteracy, a very poor health care system, and a scarce Intensive Care Unit. A series of studies have reported clinical characteristics of COVID-19 critical illness [7] and severe illness [8] patients. The clinical features and risk factors considered aims for the identification of risk factors associated with fatal outcomes. Regardless of the scientist’s effort to better understand the diagnostic, and clinical characteristics of the disease, our current understanding of patient’s risk factors of death with COVID-19 is still limited. Accordingly one might not exhaustively study all possible risk factors. In every study, the considered risk factors vary in number and type. Based on the literature review we studied the commonly reported
| Authors (year)       | Country | Sample size | Death | Mean (± SD) / Median [IQR] of age | Males N (%) | CVD N (%) | DM N (%) | HT N (%) | COPD N (%) | Cancer N (%) | OR or HR (95%CI) |
|---------------------|---------|-------------|-------|---------------------------------|-------------|-----------|----------|----------|------------|---------------|------------------|
| Albitar et al. [51] | Asian   | 828         | 219   | 49.4 (20.9) a                  | 489 (59.1)  | 23 (2.8)  | 62 (7.5) | 90 (10.9) | NA         | NA            | Age: Old: aOR = 1.08 (1.06–1.09)  
Sex: Male: aOR = 1.61 (1.01–2.58)  
HT: Yes: aOR = 3.58 (1.69–7.55)  
Obese: Yes: aOR = 1.78 (1.06–3.00)  
Cardiac injury: Yes: aOR = 2.01 (1.13–3.58) |
| Al-Salameh et al. [52] | France  | 432         | 89    | 72.0 (14.3) a                  | 238 (55.1)  | 148 (34.3) | 115 (26.6) | 255 (59.0) | 39 (9.02)  | NA            | Obese: Yes: aOR = 1.78 (1.06–3.00)  
Cardiac disease: Yes: aOR = 2.01 (1.13–3.58) |
| Barman et al. [50]  | Turkey  | 607         | 103   | 69.3 (12.5) a                  | 334 (55.0)  | NA        | 192 (31.6) | 266 (43.8) | 73 (12.0)  | NA            | Age: Old: aOR = 1.03 (1.01–1.05)  
HT: Yes: aOR = 1.26 (0.60–2.62)  
DM: Yes: aOR = 1.39 (0.89–2.17)  
Cardiac injury: Yes: aOR = 10.58 (2.42–46.27) |
| Berenguer et al. [49] | Spain   | 4035        | 1131  | 70 [56–80]                      | 2433 (61.0) | 932 (23.3) | 871 (21.8) | 2052 (51.2) | 715 (17.9) | NA            | Age: Old: aHR = 2.72 (1.74–4.23)  
HT: Yes: aHR = 1.29 (1.13–1.49)  
Obese: Yes: aHR = 1.53 (1.28–1.84)  
Cancer: Yes: aHR = 1.49 (1.24–1.79) |
| Caliskan and Saylan [82] | Turkey  | 565         | 75    | 48 (19.67)                      | NA          | NA        | 72 (12.7) | 128 (22.7) | 37 (6.5)   | NA            | Age: Old: aOR = 1.05 (1.03–1.11)  
Smoking: Yes: aHR = 6.51 (2.73–15.5)  
COPD: Yes: aOR = 3.21 (1.22–8.43) |
| Chen et al. [46]    | China   | 1390        | 50    | 69 [51–86]                      | 904 (56.8)  | 30 (19)   | 130 (8.2) | 269 (16.9) | 24 (1.5)   | NA            | Age: Old: aHR = 3.43 (1.24–9.50)  
CVD: Yes: aHR = 3.10 (1.07–8.94) |
| Authors (year)   | Country | Sample size | Death Mean (± SD) / Median [IQR] of age | Males N (%) | CVD N (%) | DM N (%) | HT N (%) | COPD N (%) | Cancer N (%) | OR or HR (95%CI) |
|-----------------|---------|-------------|---------------------------------------|-------------|-----------|----------|----------|-------------|--------------|-----------------|
| Chen et al. [47]| China   | 1859        | 208 59 [45–68]                         | 925 (50)    | NA        | 262 (14) | 579 (31) | 61 (3)      | 69 (4)       | Age: Old: aHR = 1.04 (1.03–1.06) Smoking: Yes: aHR = 1.84 (1.17–2.92) D-dimer: High: aHR = 3.00 (2.17–4.16) |
| Chen et al. [48]| China   | 3309        | 307 62 [51–69]                         | 1642 (51.5) | 242 (73)  | 464 (14) | 988 (29.9)| 42 (1.3)    | NA           | Age: Old: aOR = 9.08 (4.44–18.59) Sex: Female: aOR = 0.44 (0.34–0.58) HT: Yes: aOR = 1.14 (0.87–1.50) DM: Yes: OR = 0.87 (0.70–1.36) CVD: Yes: aOR = 1.41 (0.94–2.13) COPD: Yes: aOR = 1.72 (0.80–3.71) Kidney disease: Yes: aOR = 2.85 (1.42–5.73) |
| Chilimuri et al. [45]| USA    | 375         | 160 63 [52–72]                         | 236 (63)    | 62 (17)   | 175 (47) | 225 (60) | NA          | NA           | Age: Old: aOR = 1.04 (1.01–1.06) CVD: Yes: aOR = 1.56 (0.78–3.11) HT: Yes: aOR = 2.43 (1.57–3.77) DM: Yes: aOR = 1.96 (1.29–2.98) D-dimer: High: aOR = 3.16 (1.75–5.73) |
| Colombi et al. [55]| Italy  | 236         | 108 68 [66–70]                         | 177 (75)    | 127 (54)  | 37 (16)  | NA       | NA          | 35 (1.5)     | Age: Old: aOR = 3.4 (1.7–6.6) Cancer: Yes: aOR = 3.5 (1.6–7.7) CVD: Yes: aOR = 3.7 (1.9–7.3) |
| Authors (year) | Country | Sample size | Death Mean (± SD) / Median [IQR] | Males N (%) | CVD N (%) | DM N (%) | HT N (%) | COPD N (%) | Cancer N (%) | OR or HR (95%CI) |
|---------------|---------|-------------|----------------------------------|-------------|-----------|----------|----------|------------|---------------|-----------------|
| Cummings et al. [71] | USA | 257 | 101 | 62 [51–72] | 171 (67) | 49 (19) | 92 (36) | 162 (63) | 24 (9) | NA |
| Du et al. [44] | China | 179 | 21 | 57.6 (13.7) \(^a\) | 97 (54.2) | 29 (16.2) | 33 (18.4) | 58 (32.4) | NA | 2 (2.2) |
| Fabio et al. [43] | Italy | 410 | 95 | 65 [56–75] | 299 (72.9) | 51 (12.6) | 69 (17.0) | 203 (49.9) | 22 (5.4) | 22 (5.4) |
| Grasselli et al. [42] | Italy | 3988 | 1926 | 63 [55–69] | 3188 (79.9) | 538 (13.5) | 514 (12.9) | 1643 (41.2) | 93 (2.3) | 331 (8.3) |

Age: Old: aHR = 1.31 (1.09–1.57)  
Sex: Male: aHR = 1.13 (0.71–1.81)  
HT: Yes: aHR = 1.58 (0.89–2.81)  
DM: Yes: aHR = 1.31 (0.81–2.10)  
COPD: Yes: aHR = 2.94 (1.48–5.84)  
Increase D-dimer: aHR = 1.10 (1.01–1.19)  
Cardiac disease: Yes: aHR = 1.76 (1.08–2.86) 
CVD: Yes: aOR = 2.46 (1.80–3.35)  
Cardiac disease: Yes: aOR = 4.07 (1.78–9.35) 
Cancer: Yes: aHR = 2.32 (1.15–4.64)  
DM: Yes: aHR = 1.51 (0.96–2.35) 
COPD: Yes: aHR = 1.68 (1.28–2.19)
| Authors (year)          | Country | Sample size | Death | Mean (± SD) / Median [IQR] of age | Males N (%) | CVD N (%) | DM N (%) | HT N (%) | COPD N (%) | Cancer N (%) | OR or HR (95%CI) |
|------------------------|---------|-------------|-------|---------------------------------|-------------|-----------|----------|----------|------------|--------------|-----------------|
| Guan et al. [41]       | China   | 1590        | 131   | 48.9 (16.3) a                   | 904 (57.3)  | 59 (3.7)  | 130 (8.2) | 269 (16.9)| 24 (1.5)   | 18 (1.1)     |                  |
|                        |         |             |       |                                 |             |           |          |          |            |              |                  |
| Hernández-Galdamez et al. [40] | Mexico | 211,003     | 7135  | 45.7 (16.3) a                   | 115,442 (54.7) | 4949 (2.35) | 34,685 (16.4) | 42,453 (20.1) | 3721 (1.8) | 530 (15.6) |                  |
|                        |         |             |       |                                 |             |           |          |          |            |              |                  |
| Klang et al. [39]      | USA     | 3406        | 1076  | 76.0 [67–84]                    | 1961 (57.6) | 513 (15.1) | 1599 (46.9) | 2299 (67.5) | NA         | 530 (15.6) |                  |
|                        |         |             |       |                                 |             |           |          |          |            |              |                  |
| Kuderer et al. [38]    | USA     | 928         | 121   | 66 [57–76]                      | 468 (50.4)  | NA        | NA       | NA       | NA         | 294 (31.7)   |                  |
|                        |         |             |       |                                 |             |           |          |          |            |              |                  |
| Lee et al. [37]        | Korea   | 98          | 20    | 72 [68–79]                      | 44 (44.9)   | 16 (16.3) | 27 (27.6) | 52 (53.1) | NA         | 11 (11.2)    |                  |
| Authors (year) | Country | Sample size | Death | Mean (± SD) / Median [IQR] of age | Males N (%) | CVD N (%) | DM N (%) | HT N (%) | COPD N (%) | Cancer N (%) | OR or HR (95%CI) |
|---------------|---------|-------------|-------|---------------------------------|-------------|----------|---------|---------|-----------|-------------|-----------------|
| Lee et al. [36] | UK      | 800         | 226   | 69 [59–76]                      | 449 (56)    | 109 (14) | 131 (16) | 247 (31) | 61 (8)     | NA          | Age: Old: aOR = 9.42 (6.56–10.02) Sex: Male: aOR = 1.67 (1.19–2.34) HT: Yes: aOR = 1.95 (1.36–2.80) DM: Yes: aOR = 1.61 (1.03–2.48) CVD: Yes: aOR = 2.32 (1.47–3.64) COPD: Yes: aOR = 1.80 (1.01–2.77) |
| Li et al. [35]  | China   | 548         | 87    | 60 [48–69]                      | 276 (509)   | 34 (6.2) | 83 (15.1) | 166 (30.3) | 17 (3.1)   | 24 (4.7)    | Age: Old: aHR = 1.72 (1.05–2.85) Sex: Male: aHR = 1.72 (1.09–2.73) Cardiac injury: Yes: aHR = 2.92 (1.80–4.76) |
| Lim et al. [34] | Korea   | 160         | 44    | 67 [24–92]                      | 86 (53.8)   | 21 (13.1) | 50 (31.3) | 78 (48.1)  | NA         | NA          | Age: Old: aHR = 1.04 (1.01–1.07) Kidney disease: Yes: aHR = 3.62 (1.75–7.48) Sex: Male: aHR = 0.61 (0.32–1.16) HT: Yes: aHR = 1.34 (0.71–2.52) DM: Yes: aHR = 1.35 (0.72–2.56) |
| Mehra et al. [33] | North America, Asia and Europe | 8910 | 515 | 490 (16.0) a | 5339 (599) | NA | 1272 (14.3) | 2349 (26.3) | 225 (2.5) | NA | Age: Old: aOR = 1.93 (1.60–2.41) Sex: Male: aOR = 1.26 (1.05–1.54) COPD: Yes: aOR = 2.96 (2.00–4.40) Smoking: Yes: aOR = 1.79 (1.29–2.47) CVD: Yes: aOR = 2.48 (1.62–2.47) |
### Table 1 (continued)

| Authors (year) | Country | Sample size | Death (Mean ± SD / Median [IQR] of age) | Males N (%) | CVD N (%) | DM N (%) | HT N (%) | COPD N (%) | Cancer N (%) | OR or HR (95%CI) |
|----------------|---------|-------------|-----------------------------------------|-------------|-----------|----------|----------|------------|-------------|------------------|
| Mikami et al. [32] | USA     | 6493        | 858 (59) [43, 72]                        | 3538 (54.5) | NA        | 1151 (17.7) | 1637 (25.2) | 176 (2.7) | 413 (6.4) | Age: Old: aHR = 4.85 (2.75–8.56)  
Sex: Male: aHR = 1.22 (1.11–1.33)  
HT: Yes: aHR = 0.91 (0.79–1.07)  
DM: Yes: aHR = 0.92 (0.73–1.16)  
Cancer: Yes: aHR = 1.08 (0.84–1.40)  
D-dimer: High: aHR = 1.19 (1.02–1.39) |
| Palaiodimos et al. [31] | USA     | 200         | 48 (64) [50–74]                         | 98 (49)     | 22 (1.1)  | 79 (39.5) | 152 (76) | 28 (14) | NA        | Age: Old: aOR = 1.73 (1.25–5.98)  
Sex: Male: aOR = 2.74 (1.25–5.93)  
DM: Yes: aOR = 1.16 (0.55–2.44)  
BMI: Obese: aOR = 3.78 (1.45–9.83)  
COPD: Yes: aOR = 2.05 (0.76–5.51) |
| Parra-Bracamonte et al. [30] | Mexico | 142,690     | 16872 (44) [33–56]                     | 79,280 (56) | NA        | 23,803 (1.7) | 28,874 (20) | 2655 (2) | NA        | Age: Old: aOR = 3.73 (2.99–4.65)  
Sex: Male: aOR = 1.45 (1.39–1.50)  
HT: Yes: aOR = 1.24 (1.19–1.29)  
DM: Yes: aOR = 1.28 (1.24–1.34)  
COPD: Yes: aOR = 1.26 (1.15–1.38)  
Obese: Yes: aOR = 1.23 (1.17–1.28)  
Kidney disease: Yes: aOR = 1.8 (1.66–1.96) |
| Authors (year)  | Country | Sample size | Death Mean (± SD) / Median [IQR] of age | Males N (%) | CVD N (%) | DM N (%) | HT N (%) | COPD N (%) | Cancer N (%) | OR or HR (95%CI) |
|-----------------|---------|-------------|----------------------------------------|-------------|-----------|----------|---------|------------|--------------|----------------|
| Petrilli et al. [29] | USA     | 5279        | 665 54 [38–66]                          | 2615 (49.5) | 2752 (52.1) | 1195 (22.6) | 2256 (42.7) | 786 (14.9) | 403 (7.6)  | Age: Old: aHR = 7.69 (4.60–12.84)  
       |         |             |                                        |             |           |          |         |            |              | Sex: Male: aHR = 1.27 (1.08–1.50)  
       |         |             |                                        |             |           |          |         |            |              | HT: Yes: aHR = 0.94 (0.76–1.16)  
       |         |             |                                        |             |           |          |         |            |              | Obese: Yes: aHR = 1.41 (0.98–2.01)  
       |         |             |                                        |             |           |          |         |            |              | DM: Yes: aHR = 1.10 (0.93–1.31)  
       |         |             |                                        |             |           |          |         |            |              | COPD: Yes: aHR = 0.93 (0.76–1.15)  
       |         |             |                                        |             |           |          |         |            |              | Cancer: Yes: aHR = 1.31 (1.05–1.62)  
       |         |             |                                        |             |           |          |         |            |              | Kidney disease: Yes: aHR = 1.18 (0.97–1.43)  |
| Pettit et al. [28] | USA     | 238         | 24 58.5 (17.0)                          | 113 (47.5)  | 51 (21.4) | 68 (28.6) | 126 (52.9) | NA         | 27 (11.3)  | Age: Old: aOR = 3.6 (2.0–6.3)  
       |         |             |                                        |             |           |          |         |            |              | Obese: Yes: aOR = 1.7 (1.1–2.8)  |
| Price-Haywood et al. [27] | Australia | 3481        | 326 55.5 (18.5)                         | 1394 (400)  | NA        | 566 (16.3) | 1074 (30.8) | 79 (2.3)   | 158 (4.5)  | Age: Old: aOR = 1.19 (1.13–1.24)  
       |         |             |                                        |             |           |          |         |            |              | Sex: Male: aOR = 1.61 (1.28–2.04)  
       |         |             |                                        |             |           |          |         |            |              | Obese: Yes: aOR = 1.05 (0.83–1.34)  |
| Priyank et al. [26] | USA     | 522         | 92 63 [50–72]                           | 218 (41.8)  | 70 (13.4) | 221 (42.3) | 416 (79.7) | 47 (9)     | 48 (9.2)   | Age: Old: aOR = 3.1 (1.7–5.6)  
       |         |             |                                        |             |           |          |         |            |              | Sex: Male: aOR = 2.44 (1.43–4.17)  
       |         |             |                                        |             |           |          |         |            |              | HT: Yes: aOR = 3.36 (1.3–8.6)  
       |         |             |                                        |             |           |          |         |            |              | DM: Yes: aOR = 1.51 (0.9–2.6)  
       |         |             |                                        |             |           |          |         |            |              | COPD: Yes: aOR = 1.48 (0.65–3.34)  
       |         |             |                                        |             |           |          |         |            |              | Kidney disease: Yes: aOR = 1.08 (0.51–2.28)  
       |         |             |                                        |             |           |          |         |            |              | Cancer: Yes aOR = 0.48 (0.20–1.10)  |
Table 1 (continued)

| Authors (year)          | Country | Sample size | Death | Mean (± SD) / Median [IQR] of age | Males N (%) | CVD N (%) | DM N (%) | HT N (%) | COPD N (%) | Cancer N (%) | OR or HR (95%CI) |
|-------------------------|---------|-------------|-------|----------------------------------|-------------|-----------|----------|----------|------------|--------------|-------------------|
| Regalado-Artamendi et al. [74] | Spain   | 177         | 61    | 70 [56–77]                        | 99 (55.9)   | NA        | 33 (18.6) | 73 (41.2) | NA         | NA           | Age: Old: aHR = 1.05 (1.03–1.07) Sex: Male: aHR = 1.07 (0.65–1.77) HT: Yes: aHR = 1.79 (1.09–2.96) DM: Yes: aHR = 1.13 (0.60–2.10) Kidney disease: Yes: aHR = 2.36 (1.04–5.38) D-dimer: High: aOR = 1.26 (1.01–1.56) |
| Rivera-Izquierdo et al. [25] | Spain   | 238         | 61    | 64.7 (15.4)a                      | 131 (55.0)  | 54 (22.7) | 52 (21.9) | 116 (48.7) | NA         | NA           | Age: Old: aHR = 1.09 (1.07–1.11) Sex: Male: aHR = 1.34 (0.80–2.27) DM: Yes: aHR = 2.33 (1.38–3.94) |
| Shi et al. [23]          | China   | 416         | 57    | 64 [21–95]                        | 205 (49.3)  | 44 (10.6) | 60 (14.4) | 127 (30.5) | 12 (2.9)   | 9 (2.2)      | Age: Old: aHR = 1.02 (0.99–1.05) CVD: Yes: aHR = 1.51 (0.70–3.30) COPD: Yes: aHR = 0.37 (0.04–3.50) Cardiac disease: Yes: aHR = 4.26 (1.92–9.49) |
| Soares et al. [22]       | Brazil  | 10,713      | 821   | NA                               | 4804 (44.8) | 2541 (23.7)| 1100 (10.3) | NA        | NA         | NA           | Age: Old: aOR = 3.95 (2.95–5.33) CVD: Yes: aOR = 2.02 (1.59–2.57) DM: Yes: aOR = 1.68 (1.10–3.09) |
| Su et al. [54]           | China   | 172         | 32    | 71.6 (11.0) a                     | 121 (70.3)  | 21 (12.2) | 18 (10.5) | 18 (11)  | 6 (3.4)    | 3 (1.7)      | HT: Yes: OR = 3.5 (1.1–10.8) DM: Yes: OR = 1.9 (0.6–5.8) Sex: Male: OR = 1.53 (0.75–3.13) CVD: Yes: OR = 5.1 (1.7–15.5) |
| Authors (year)                | Country | Sample size | Death | Mean (± SD) / Median [IQR] of age | Males N (%) | CVD N (%) | DM N (%) | HT N (%) | COPD N (%) | Cancer N (%) | OR or HR (95%CI) |
|------------------------------|---------|-------------|-------|----------------------------------|-------------|-----------|----------|----------|------------|--------------|------------------|
| van Gerwen et al. [21]       | USA     | 3703        | 616   | 56.8 (18.2) a                    | 2049 (55.3) | 292 (7.9) | 1045 (28.2) | 1643 (44.4) | 172 (4.6)  | 312 (8.4)   | Age: Old: aOR = 5.29 (2.51–11.15) Sex: Male: aOR = 1.46 (1.17–1.82) HT: Yes: aOR = 1.87 (1.53–2.29) DM: Yes: aOR = 1.62 (1.34–1.96) CVD: Yes: aOR = 1.47 (1.06–2.02) Smoking: Yes: aOR = 1.06 (0.66–1.72) |
| Wang et al. [20]              | China   | 339         | 65    | 69 [65–76]                       | 166 (49)    | 53 (15.7) | 54 (16)  | 138 (40.8) | 21 (6.2)   | 15 (4.4)     | Age: Old: aHR = 1.06 (1.03–1.09) CVD: Yes: aHR = 1.85 (1.06–3.26) COPD: Yes: aHR = 2.24 (1.12–4.97) |
| Wu et al. [53]                | China   | 201         | 44    | 51 [43–60]                       | 128 (64)    | 8 (4)     | 22 (11)  | 39 (19.4)  | NA         | 1 (0.5)      | Age: Old: HR = 6.17 (3.26–11.67) HT: Yes: HR = 1.70 (0.92–3.14) DM: Yes: HR = 1.58 (0.80–3.13) D-dimer: High: HR = 1.02 (1.01–1.04) |
| Xu et al. [19]                | China   | 239         | 147   | 62.5 (13.3) a                    | 143 (59.8)  | NA        | 44 (18.4) | 105 (43.9) | NA         | NA           | Age: Old: aHR = 1.57 (1.12–2.19) Cardiac injury: Yes: aHR = 0.88 (0.57–1.34) Kidney disease: Yes: aHR = 2.06 (1.36–3.10) |
| Yao et al. [18]               | China   | 248         | 17    | 63.0 (13.4) a                    | NA          | NA        | 44 (17.7) | 78 (31.5)  | NA         | NA           | Age: Old: aOR = 1.04 (0.98–1.10) D-dimer: High: aOR = 10.17 (1.10–29.38) |

**Table 1** (continued)
Table 1 (continued)

| Authors (year) | Country | Sample size | Death Mean (± SD) / Median [IQR] | Males N (%) | CVD N (%) | DM N (%) | HT N (%) | COPD N (%) | Cancer N (%) | OR or HR (95%CI) |
|----------------|---------|-------------|----------------------------------|-------------|-----------|----------|----------|------------|--------------|-----------------|
| Yu et al. [83] | China   | 1464        | 212 64 [51–71]                  | 736 (51.3)  | 47 (3.2)  | 211 (14.4) | 306 (20.9) | 50 (3.4)   | 17 (1.2)     | Sex: Male: aOR = 1.97 (1.29–2.99) |
|                |         |             |                                  |             |           |          |          |            |              | Age: Old: aOR = 2.15 (1.35–3.43) |
|                |         |             |                                  |             |           |          |          |            |              | HT: Yes: aOR = 1.08 (0.68–1.72)   |
|                |         |             |                                  |             |           |          |          |            |              | DM: Yes: aOR = 2.34 (1.45–3.76)   |
| Zhou et al. [17]| China   | 191         | 54 56 [46–67]                   | 119 (62)    | 15 (8)    | 36 (19)  | 58 (30)  | 6 (3)      | NA           | Age: Old: aOR = 1.10 (1.03–1.17) |
|                |         |             |                                  |             |           |          |          |            |              | D-dimer: High aOR = 18.42 (2.64–29.39) |

aHR adjusted hazard ratio, aOR adjusted odds ratio, CVD cerebrovascular disease, HT hypertension, COPD chronic obstructive pulmonary disease, DM diabetes, COVID-19 coronavirus disease 2019, IQR interquartile range
a Reported as mean (± SD). Other studies were reported as median (IQR)
risk factors such as hypertension, diabetes, chronic obstructive pulmonary disease, dyspnoea, history of substance use, gender, acute respiratory distress syndrome (ARDS), history of smoking, older age, albumin, and D-dimer [9–12]. The study aims to synthesize and enhance our understanding about the precision of the risk factors effect on COVID-19 fatality rate.
Methods

Study protocol
To examine the association between COVID-19 mortality versus in with comorbidities, gender, smoking status, obesity, age, acute kidney injury, and D-dimer, we followed PRISMA guidelines [13] to perform the meta-analysis of the articles identified through our systematic reviews.

Search strategy
Electronic databases including Google Scholar, Cochrane Library, Web of Sciences (WOS), EMBASE, Medline/PubMed, COVID-19 Research Database (WHO), COVID-19 Open Research Dataset Challenge, and Scopus, were systematically searched till 31 August 2020. The search strategy was as follows: (“severe acute respiratory syndrome coronavirus 2” or “novel coronavirus” or “COVID-19” or “2019-nCoV” or “SARS-CoV-2”) and (“survival” or “fatal outcome” or “mortality” or “death”). Furthermore, the search was specifically focused on articles that analyzed laboratory parameters, pre-existing comorbidities, clinical status, and demographic characteristics as potential predictors for fatal outcome of COVID-19. No restriction was applied on time and language of publications. In order to improve the screening process and save time, we downloaded the literature results into EndNote X9.

Eligibility criteria
Once duplicates were removed, the initial search results were screened for relevance by titles and abstracts by both authors. The full texts were reviewed for the eligibility criteria (Fig. 1). Studies without abstract and/or full text, Correspondence letters, COVID-19 studies on children only, editorials, reviews, qualitative studies, books, theses, expert opinion papers, and review articles were excluded from the analysis. Furthermore, among the eligible studies, we used if only the study reported odds ratios (ORs) or hazard ratios (HRs) along with 95% CI for the association between demographic or epidemiological or clinical characteristics and fatal outcome of coronavirus.

Table 2 Results of the subgroup analysis based on demographic and clinical variables associated with coronavirus mortality

| Risk factors       | Effect measures | Numbers of study | Effect size (95% CI) | Heterogeneity | Begg’s test P-value | Egger’s test P-value |
|--------------------|-----------------|------------------|----------------------|---------------|---------------------|----------------------|
|                    |                 |                  |                      |               |                     |                      |
| Older age          | pOR             | 21               | 2.61 (1.75–3.47)     | 99.97         | 0.000               | 0.321                |
|                    | pHR             | 16               | 1.31 (1.11–1.51)     | 99.59         | 0.000               | 0.212                |
| Gender: Male vs Female | pOR       | 15               | 1.45 (1.41–1.51)     | 66.63         | 0.000               | 0.243                |
| Smoking status: Yes vs No | pOR | 9                | 1.24 (1.07–1.41)     | 62.45         | 0.000               | 0.424                |
|                    | pHR             | 5                | 1.42 (1.01–1.83)     | 55.81         | 0.000               | 0.143                |
| Obesity: Yes vs No | pOR             | 9                | 1.34 (1.17–1.52)     | 82.56         | 0.000               | 0.293                |
|                    | pHR             | 2                | 1.50 (1.26–1.75)     | 36.82         | 0.000               | 0.253                |
| CVDs: Yes vs No    | pOR             | 9                | 1.83 (1.50–2.17)     | 41.27         | 0.020               | 0.410                |
|                    | pHR             | 3                | 1.77 (0.95–2.59)     | 13.73         | 0.000               | 0.426                |
| Diabetes           | pOR             | 13               | 1.52 (1.36–1.69)     | 79.83         | 0.000               | 0.432                |
|                    | pHR             | 10               | 1.17 (1.02–1.32)     | 49.45         | 0.000               | 0.298                |
| Hypertension       | pOR             | 12               | 1.57 (1.27–1.87)     | 94.97         | 0.000               | 0.114                |
|                    | pHR             | 8                | 1.18 (1.01–1.40)     | 66.66         | 0.000               | 0.054                |
| COPD               | pOR             | 7                | 1.58 (1.08–2.07)     | 92.24         | 0.000               | 0.130                |
|                    | pHR             | 5                | 1.71 (1.01–2.45)     | 78.28         | 0.000               | 0.092                |
| Cancer             | pOR             | 3                | 1.43 (0.06–2.80)     | 79.98         | 0.000               | 0.181                |
|                    | pHR             | 5                | 1.33 (1.09–1.56)     | 58.67         | 0.000               | 0.461                |
| Acute kidney injury| pOR             | 5                | 1.87 (1.48–2.26)     | 86.53         | 0.000               | 0.131                |
|                    | pHR             | 3                | 2.21 (1.44–2.99)     | 42.43         | 0.030               | 0.256                |
| Cardiac injury     | pOR             | 3                | 2.33 (0.88–3.79)     | 59.77         | 0.320               | 0.088                |
|                    | pHR             | 4                | 1.89 (0.75–3.02)     | 76.57         | 0.000               | 0.065                |
| Increased D-dimer  | pOR             | 3                | 10.49 (1.80–19.18)   | 96.14         | 0.000               | 0.312                |
|                    | pHR             | 5                | 1.44 (1.01–2.06)     | 91.52         | 0.000               | 0.067                |

Keys: (\(H_0\)) there are no small study effects, pOR pooled odds ratio, pHR pooled hazard ratio
### Odds ratio

| Study                        | Effect Size with 95% CI | Weight (%) |
|------------------------------|------------------------|------------|
| Albitar et al. (2020)        | 1.05 [1.06, 1.10]      | 3.42       |
| Barman et al. (2020)         | 1.03 [1.01, 1.05]      | 3.42       |
| Chen J et al. (2020)         | 9.08 [4.44, 18.59]     | 0.50       |
| Chilimuri et al. (2020)      | 1.04 [1.01, 1.06]      | 3.42       |
| Colombi et al. (2020)        | 3.40 [1.70, 6.60]      | 2.01       |
| Du et al. (2020)             | 3.77 [1.20, 11.80]     | 0.60       |
| Klang et al. (2020)          | 1.70 [1.60, 1.80]      | 3.42       |
| Kuderer et al. (2020)        | 1.84 [1.53, 2.21]      | 3.37       |
| Lee L et al. (2000)          | 9.42 [6.56, 12.02]     | 2.53       |
| Mehra et al. (2020)          | 1.93 [1.60, 2.41]      | 3.36       |
| Palaiodimos et al. (2020)    | 1.73 [1.25, 2.98]      | 2.07       |
| Parra-Bracamonte et al. (2020)| 3.73 [2.99, 4.65]  | 3.17       |
| Pettit et al. (2020)         | 3.60 [2.00, 6.30]      | 2.22       |
| Price-Haywood et al. (2020)  | 1.19 [1.13, 1.24]      | 3.42       |
| Priyank et al. (2020)        | 3.10 [1.70, 5.60]      | 2.37       |
| Shah et al. (2020)           | 3.10 [1.70, 5.60]      | 2.37       |
| Soares et al. (2020)         | 3.95 [2.95, 5.33]      | 2.93       |
| van Gerwen et al. (2020)     | 5.29 [2.51, 11.15]     | 1.08       |
| Yao et al. (2020)            | 1.04 [0.98, 1.10]      | 3.42       |
| Yu et al. (2020)             | 2.15 [1.35, 3.43]      | 3.04       |
| Zhou et al. (2020)           | 1.10 [1.03, 1.17]      | 3.42       |

Heterogeneity: $I^2 = 3.30$, $I^2 = 99.97\%$, $H^2 = 3483.00$

### Hazard ratio

| Study                        | Effect Size with 95% CI | Weight (%) |
|------------------------------|------------------------|------------|
| Berenguer et al. (2020)      | 2.72 [1.74, 4.23]      | 2.90       |
| Chen L et al. (2020)         | 1.04 [1.03, 1.06]      | 3.42       |
| Chen R et al. (2020)         | 3.43 [1.24, 9.50]      | 1.14       |
| Cummings et al. (2020)       | 1.31 [1.09, 1.57]      | 3.40       |
| Fabio et al. (2020)          | 3.17 [1.84, 5.44]      | 2.48       |
| Grasselli et al. (2020)      | 1.75 [1.60, 1.92]      | 3.41       |
| Li et al. (2020)             | 1.72 [1.05, 2.85]      | 3.12       |
| Lim et al. (2020)            | 1.04 [1.01, 1.07]      | 3.42       |
| Mikami et al. (2020)         | 4.85 [2.75, 8.56]      | 1.72       |
| Petrilli et al. (2020)        | 7.69 [4.60, 12.84]     | 1.15       |
| Rivera-Izquierdo et al. (2020)| 1.09 [1.07, 1.12]  | 3.42       |
| Shi et al. (2000)            | 1.02 [0.99, 1.05]      | 3.42       |
| Wang L et al. (2020)         | 1.06 [1.03, 1.10]      | 3.42       |
| Regalado-Artamendi et al. (2021)| 1.05 [1.03, 1.07]  | 3.42       |
| Wu et al. (2020)             | 6.17 [3.26, 11.67]     | 1.12       |
| Xu et al. (2020)             | 1.57 [1.12, 2.19]      | 3.31       |

Heterogeneity: $I^2 = 0.09$, $I^2 = 99.54\%$, $H^2 = 216.98$

**Fig. 3** Forest plot showing the estimate for the effects of age on COVID-19 mortality
Data extraction and assessment for study quality
Both authors independently examined the downloaded EndNote X9 search outputs eligibility for inclusion. Any disagreements between the authors were resolved through discussion and mutual agreement. Both authors extracted the following data: the first author’s name, countries, assessment methods, sample size, study design, the publication year, demographic variables (e.g., gender, age, etc.), clinical variables (e.g., comorbidities, complications, D-dimer, etc.), outcome (mortality), exposure (risk factors), and adjusted odds ratios or hazard ratios or relative risk. The authors independently evaluated the quality methodological approach of the articles using a Newcastle–Ottawa technique [14]. In this technique, three main components were utilized to assess the quality of the papers such as assessment of the outcome, comparability of the study groups, and selection procedure of the study patients. The Newcastle–Ottawa technique included seven domains, each one of these domains were scored from 3 to 0 (i.e., from low to high bias) and their average score were taken.

Statistical analysis
We have used peer-reviewed and published ORs or HRs (and their 95%CI) for the association between the fatal outcome of COVID-19 and risk factors. A mixed-effect
model has been computed keeping into consideration the expected between-study heterogeneity. Heterogeneity in effect sizes was assessed by computing Cochran’s Q test; a significant Q indicates a lack of homogeneity and inference of heterogeneity. The proportion of the total variance attributable to the study heterogeneity was determined using $I^2$ statistic [15]. The $I^2$ values of 60–90%, 40–59%, and 0–39% were considered to indicate severe, moderate, and mild, respectively [15]. Funnel plots with Egger weighted regression test were used for assessing publication bias [16]. All of the analyses were implemented with the statistical software’s R-4.0.2 and

![Fig. 5 Forest plot showing the estimate for the effects of smoking status and obesity on COVID-19 mortality](image)

### A) Obese: Yes vs No

| Study                          | Effect Size with 95% CI | Weight (%) |
|--------------------------------|-------------------------|------------|
| Al-Salameh et al. (2020)       | 1.78 [ 1.06, 3.00]      | 2.21       |
| Hernández-Galdamez et al. (2020)| 1.42 [ 1.37, 1.47]      | 26.09      |
| Klang et al. (2020)            | 1.60 [ 1.20, 2.30]      | 5.86       |
| Palalodimos et al. (2020)      | 3.78 [ 1.45, 9.83]      | 0.13       |
| Parra-Bracamonte et al. (2020) | 1.23 [ 1.17, 1.28]      | 25.93      |
| Pettit et al. (2020)           | 1.70 [ 1.10, 2.80]      | 2.81       |
| Price-Haywood et al. (2020)    | 1.05 [ 0.83, 1.34]      | 15.17      |
| Priyanka et al. (2020)         | 2.29 [ 1.11, 4.69]      | 0.69       |
| Shah et al. (2020)             | 2.29 [ 1.11, 4.69]      | 0.69       |
| Heterogeneity: $t^2 = 0.03$, $I^2 = 82.56\%$, $H^2 = 5.73$ | 1.34 [ 1.17, 1.52] |            |

| Study                          | Effect Size with 95% CI | Weight (%) |
|--------------------------------|-------------------------|------------|
| Berenguer et al. (2020)        | 1.53 [ 1.28, 1.84]      | 13.93      |
| Petrilii et al. (2020)         | 1.41 [ 0.98, 2.01]      | 6.49       |
| Heterogeneity: $t^2 = 0.08$, $I^2 = 36.82\%$, $H^2 = 1.58$ | 1.50 [ 1.26, 1.75] |            |

### B) Smoking status: Yes vs No

| Study                          | Effect Size with 95% CI | Weight (%) |
|--------------------------------|-------------------------|------------|
| Kuderer et al. (2020)          | 1.60 [ 1.03, 2.47]      | 17.95      |
| Mehra et al. (2020)            | 1.79 [ 1.29, 2.47]      | 23.01      |
| Shah et al. (2020)             | 1.03 [ 0.55, 1.95]      | 18.63      |
| van Gerwen et al. (2020)       | 1.06 [ 0.66, 1.72]      | 25.90      |
| Caliskan and Saylan (2020)     | 6.51 [ 2.73, 10.50]     | 0.90       |
| Heterogeneity: $t^2 = 0.18$, $I^2 = 55.81\%$, $H^2 = 2.26$ | 1.42 [ 1.01, 1.83] |            |

| Study                          | Effect Size with 95% CI | Weight (%) |
|--------------------------------|-------------------------|------------|
| Chen L et al. (2020)           | 1.84 [ 1.17, 2.92]      | 13.60      |
| Heterogeneity: $t^2 = 0.00$, $I^2 = .$, $H^2 = .$ | 1.84 [ 0.96, 2.71] |            |
STATA version 16, to estimate the pooled odds ratio and to investigate publication bias.

**Results**

**Search results**

We identified 150 publications through Google Scholar, Cochrane Library, Web of Sciences (WOS), EMBASE, Medline/PubMed, COVID-19 research database (WHO), COVID-19 open research dataset challenge, and Scopus database, of which, 14 studies that did not have numbers of hospital death, 31 reviews, 19 non-English, and 32 duplicates were excluded. Among the remaining 54 studies, twelve did not report cross-tabulation with ORs or HRs. Consequently, we got only 42 studies that satisfied all the eligibility criteria (see Fig. 1). Out of the 42 studies, thirty-nine provided adjusted hazard and odds ratios after multivariate adjustment for the covariates such as comorbidities, gender, smoking status, obesity, age, acute kidney injury, and D-dimer [17–52]. And the rest three studies provided crude hazard and odds ratios [53–55] (Table 1).

**Demographic characteristics and geographical distribution**

Table 1 presents a systematic summary of all the selected studies [2, 6–9, 12, 15, 18–21, 25, 26, 28, 30, 35, 40, 42, 45–47, 50–52, 55–68]. All the 42 studies were published in the year 2020. All included studies were conducted in COVID-19 outbreak areas from December 2019 to August 2020. The studies reported a total of 423,117 patients. Of these, 13 were performed in mainland China, 11 in USA, 2 in Spain, 2 in Mexico, 2 in Korea, 3 in Italy, 1 in France, 1 in Australia, 1 in Asia, 1 in Brazil, 1 in UK, 2 in Turkey and 2 mixed region. The sample size of enrolled patients ranged from 98 to 211,003 individuals. The proportions of male in the study samples ranged from 41.8 to 70.3%. The average age of individuals included in the studies ranged from 48.9 to 77 years. (Table 1).

**Prevalence of COVID-19 mortality**

The mixed effect meta-analysis model results are presented in Fig. 2. From this plot, we can see that the mortality rate of coronaviruses among the included studies ranges from a minimum of 3.14 (95% CI 2.34–4.12%) [46] to a maximum of 61.51 (95% CI 55.02–67.71%) [19]. Of the total 423,117 patients, 35,020 died which resulted in...
a weighted pooled overall mortality prevalence of 17.62% (95% CI, 14.26–21.57%). (Fig. 2).

Mortality-related risk factors

In the meta-analysis 32 effect sizes of the demographic characteristics were obtained from 37 studies [5, 9–12, 15, 17, 18, 20–22, 28, 29, 38, 40, 47–51, 53, 55, 56, 62, 66, 67, 69, 70] (26 162 cases of death out of 203 250 patients). Older age has shown increased risk of mortality due to coronavirus and the pooled OR and HR were 2.61 (95% CI 1.75–3.47) and 1.31 (95% CI 1.11–1.51), respectively (Table 2 and Fig. 3). Twenty-four studies evaluated the risk of COVID-19 mortality among male patients and showed a significantly higher risk and the pooled OR and HR were 1.45 (95% CI 1.41–1.51) and 1.24 (95% CI 1.07–1.41), respectively (Table 2 and Fig. 4). Coronavirus related risk of mortality was significantly associated with smoker patients when compared to non-smoker patients, (pOR = 1.42; 95% CI = 1.01–1.83) (Fig. 5B). Furthermore, the combined 11 effect sizes from 11 studies [2, 10, 21, 22, 24, 28, 31, 40, 44, 51, 56] revealed significant association between obesity and coronaviruses mortality (pOR = 1.34; 95% CI = 1.17–1.52; pHR = 1.50; 95%CI = 1.26–1.75) (Fig. 5A).

A total of 60 effect sizes of comorbidities were extracted from 34 studies [3, 9, 11, 12, 15, 18, 21–24, 27, 28, 31, 39, 40, 44, 48, 50–52, 54–57, 67, 69, 71–73] with a total of 407, 638 patients and 32, 465 death. The association between diabetes and in-hospital mortality are displayed in Table 2 and Fig. 6B. We noted that mortality among hospitalized COVID-19 patients with diabetes was higher compared to the patients without diabetes aOR = 1.52 (95% CI 1.36–1.69) and aHR = 1.17 (95% CI 1.02–1.32). Likewise, risk of mortality among hospitalized COVID-19 patients is highly influenced by patients with COPD (pOR = 1.58; 95% CI 1.08–2.02; pHR = 1.71; 95% CI 1.01–2.07) (Fig. 7A), hypertension (pOR = 1.57; 95% CI 1.27–1.87; pHR = 1.18; 95% CI 1.01–2.07) (Fig. 7A), CVD (pOR = 1.83; 95% CI 1.50–2.17) (Fig. 6A) and cancer (pHR = 1.33; 95% CI 1.09–1.56) (Fig. 8A).

In the meta-analysis of eight effect sizes from eight studies [19, 26, 30, 34, 39, 40, 48, 74], we noted that a significant positive association between acute kidney injury and COVID-19 mortality and the pooled OR and HR were 1.87 (95% CI 1.48–2.26) and 2.21 (95% CI 1.44–2.99), respectively (Fig. 9A). But acute cardiac injury association with COVID-19 fatality was not found to be significant (pOR = 2.33; 95% CI 0.88–3.79; pHR = 1.89; 95% CI 0.75–3.02) (Fig. 8B). Furthermore, the combined effect sizes from six studies [10, 17, 18, 32, 45, 53] revealed a significant association between increase D-dimer and coronaviruses mortality (pOR = 10.49;
95% CI 1.80–19.18) and (pHR = 1.44; 95% CI 1.01–2.06) (Fig. 9B).

Quality Assessment

The Newcastle–Ottawa score of the included studies was 7–9, and the quality of the articles was evaluated as high (Table 3).

Sensitivity analysis, publication bias, and heterogeneity

The $I^2$ statistics for gender, smoking status, obesity, CVDs, COPD, hypertension, cardiac injury, cancer, age, and D-dimer, had shown heterogeneities among the considered studies. From the sensitivity analysis, we noted that the overall estimates of comorbidities, gender, age, smoking status, obesity, acute kidney injury, and D-dimer on the fatal outcome of coronavirus, did not depend on a single study. Funnel plots were plotted for the included studies in the meta-analysis, which suggested that there...
**Fig. 9** Forest plot showing the estimate for the effects of acute kidney injury, and D-dimer on COVID-19 mortality

### A) Kidney Injury: Yes vs No

| Study                        | Effect Size 95% CI | Weight (%) |
|------------------------------|-------------------|------------|
| **Odds ratio**               |                   |            |
| Chen J et al. (2020)         | 2.85 [1.42, 5.73] | 2.09       |
| Hernández-Galdamez et al. (2020) | 2.31 [2.15, 2.48] | 27.05      |
| Klang et al. (2020)          | 1.70 [1.40, 2.10] | 21.70      |
| Parra-Bracamonte et al. (2020) | 1.80 [1.66, 1.96] | 27.39      |
| Priyank et al. (2020)        | 1.08 [0.51, 2.28] | 9.14       |
| Heterogeneity: $t^2 = 0.13, i^2 = 86.53\%$, $H^2 = 7.43$ | 1.87 [1.48, 2.26] |  |
| **Hazard ratio**             |                   |            |
| Lim et al. (2020)            | 3.62 [1.75, 7.48] | 1.22       |
| Regalado-Artamendi et al. (2021) | 2.36 [1.04, 5.38] | 2.06       |
| Xu et al. (2020)             | 2.06 [1.36, 3.10] | 9.36       |
| Heterogeneity: $t^2 = 0.10, i^2 = 42.43\%$, $H^2 = 1.74$ | 2.21 [1.44, 2.99] |  |

### B) Increase D-dimer

| Study                        | Effect Size 95% CI | Weight (%) |
|------------------------------|-------------------|------------|
| **Odds ratio**               |                   |            |
| Chilimiri et al. (2020)      | 3.16 [1.75, 5.73] | 12.48      |
| Yao et al. (2020)            | 10.17 [1.10, 29.38] | 11.77     |
| Zhou et al. (2020)           | 18.42 [2.64, 29.39] | 11.78     |
| Heterogeneity: $t^2 = 56.50$, $i^2 = 96.14\%$, $H^2 = 25.92$ | 10.49 [1.80, 19.18] |  |
| **Hazard ratio**             |                   |            |
| Chen L et al. (2020)         | 3.00 [2.17, 4.16] | 12.76      |
| Cummings et al. (2020)       | 1.10 [1.03, 1.20] | 12.85      |
| Mikami et al. (2020)         | 1.19 [1.03, 1.39] | 12.72      |
| Regalado-Artamendi et al. (2021) | 1.26 [1.01, 1.56] | 12.84      |
| Wu et al. (2020)             | 1.02 [1.01, 1.04] | 12.79      |
| Heterogeneity: $t^2 = 0.37$, $i^2 = 91.52\%$, $H^2 = 11.80$ | 1.44 [1.01, 2.06] |  |
Fig. 10 Funnel plot for publication bias of effect of comorbidities, age, smoking status, obesity, acute kidney injury, gender, and D-dimer on fatal outcome of COVID-19.
Table 3  Risk of bias assessment of 42 studies included in the meta-analysis by the Newcastle–Ottawa Scale

| Authors (year)               | Selection (4) | Comparability of Cohorts (2) | Outcome (3) | Total |
|------------------------------|---------------|------------------------------|-------------|-------|
|                              | Representativeness of exposed cohort | Selection of non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at the start of study | Study control for age and sex | Additional factors controlled for ≥ 2 variables including comorbidities | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow-up of cohorts |
| Albritar et al. [51]         | 1             | 1                            | 1           | 1     | 2     | 1           | 1    | 1    | 1   | 9    |
| Al-Salameh et al. [52]       | 1             | 1                            | 1           | 1     | 0     | 1           | 1    | 1    | 1   | 7    |
| Barman et al. [50]           | 1             | 1                            | 1           | 1     | 2     | 1           | 1    | 1    | 1   | 9    |
| Berenguer et al. [49]        | 1             | 1                            | 1           | 1     | 2     | 1           | 1    | 1    | 1   | 9    |
| Caliskan and Saylan [82]     | 1             | 1                            | 1           | 1     | 1     | 1           | 1    | 1    | 1   | 8    |
| Chen, et al. [46]            | 1             | 1                            | 1           | 1     | 0     | 1           | 1    | 1    | 1   | 7    |
| Chen et al. [47]             | 1             | 1                            | 1           | 1     | 1     | 1           | 1    | 1    | 1   | 8    |
| Chen et al. [48]             | 1             | 1                            | 1           | 1     | 2     | 1           | 1    | 1    | 1   | 9    |
| Chilimuri et al. [45]        | 1             | 1                            | 1           | 1     | 1     | 1           | 1    | 1    | 1   | 8    |
| Colombi et al. [55]          | 1             | 1                            | 1           | 1     | 1     | 1           | 1    | 1    | 1   | 8    |
| Cummings et al. [71]         | 1             | 1                            | 1           | 1     | 1     | 1           | 1    | 1    | 1   | 8    |
| Du et al. [44]               | 1             | 1                            | 1           | 1     | 1     | 1           | 1    | 1    | 1   | 8    |
| Fabio et al. [43]            | 1             | 1                            | 1           | 1     | 1     | 1           | 1    | 1    | 1   | 8    |
| Grasselli et al. [42]        | 1             | 1                            | 1           | 1     | 1     | 1           | 1    | 1    | 1   | 8    |
| Guan et al. [41]             | 1             | 1                            | 1           | 1     | 1     | 1           | 1    | 1    | 1   | 8    |
| Hernández-Galdamez et al. [40]| 1             | 1                            | 1           | 1     | 1     | 1           | 1    | 1    | 1   | 8    |
| Klang et al. [39]            | 1             | 1                            | 1           | 1     | 1     | 1           | 1    | 1    | 1   | 8    |
| Kuderer et al. [38]          | 1             | 1                            | 1           | 1     | 1     | 1           | 1    | 1    | 1   | 8    |
| Lee et al. [37]              | 1             | 1                            | 1           | 1     | 1     | 1           | 1    | 1    | 1   | 8    |
| Lee et al. [36]              | 1             | 1                            | 1           | 1     | 2     | 1           | 1    | 1    | 1   | 9    |
| Li et al. [35]               | 1             | 1                            | 1           | 1     | 1     | 1           | 1    | 1    | 1   | 8    |
| Lim et al. [34]              | 1             | 1                            | 1           | 1     | 1     | 1           | 1    | 1    | 1   | 8    |
| Mehra et al. [33]            | 1             | 1                            | 1           | 1     | 1     | 1           | 1    | 1    | 1   | 8    |
| Mikami et al. [32]           | 1             | 1                            | 1           | 1     | 1     | 1           | 1    | 1    | 1   | 8    |
Table 3 (continued)

| Authors (year) | Selection (4) | Comparability of Cohorts (2) | Outcome (3) | Total |
|----------------|---------------|-----------------------------|-------------|-------|
|                | Representativeness of exposed cohort | Selection of non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at the start of study | Study control for age and sex | Additional factors; controlled for ≥ 2 variables including comorbidities | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow-up of cohorts |       |
| Palaiodimos et al. [31] | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Parra-Bracamonte et al. [30] | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Petrilli et al. [29] | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Pettit et al. [28] | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 7 |
| Price-Haywood et al. [27] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Priyank et al. [26] | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Regalado-Artemendi et al. [74] | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Rivera-Izquierdo et al. [23] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Shah et al. [24] | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Shi et al. [23] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Soares et al. [22] | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 7 |
| Su et al. [54] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| van Gerwen et al. [21] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Wang et al. [20] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Wu et al. [53] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Xu et al. [19] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Yao et al. [18] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Yu et al. [83] | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Zhou et al. [17] | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 7 |
is no noticeable bias in the studies of our meta-analysis (Fig. 10). Besides, Begg's correlation rank and egger's regression failed to show significant publication bias (see Table 2).

Discussion

The meta-analysis of currently available regional and national reports of patients with coronavirus infection highlights the effect of complications, comorbidities, and demographic variables on mortality of coronavirus. These results have important clinical implications such as on the clinical management and specific preventive measures of coronavirus patients. Our study is by far the largest meta-analysis on COVID-19 fatality study in terms of size and coverage of complications, comorbidities, behavioural and demographic risk factors.

We found that smoking was significantly associated with the risk of mortality in coronavirus. Such a result was also reported [64] in a limited scale meta-analysis study. Accordingly, perhaps it is a high time to step up effort to advocate the danger of smoking as well as an intervention to stop smoking to reduce the overall disease burden.

Reportedly old age was significantly associated with MERS-Cov [66] and SARS [68] mortality. Likewise, our finding showed a significant association of old age with coronavirus mortality. A plausible reason for this might be some age-related chronic medical conditions and/or lower immunity level [57]. In addition, ageing affects CD4+T cells, CD8+T cells, B cells functions [75]. This age-related reduction in T cells and B cells clonal diversity is associated with impaired responses to viral infections such as influenza [76] and the excess production of type 2 cytokines could lead to prolonged pro-inflammatory immune responses and therefore perhaps contribute to poor outcomes [62].

Female with coronavirus have lower rates of hospitalization and mortality than male [77]. The results of our meta-analysis also showed that men seems to be a risk factor for COVID-19 mortality. Sex differences in both the adaptive and innate immune system have been reported previously and may account for the women advantage in coronavirus. Within the adaptive immune system, men have lower numbers of CD8+T cell [78], CD4+T cell [79] and decreased B cell production compared to women [79]. Moreover, since some important immune regulatory genes are located on the X chromosome, women patients might be advantaged due to a higher expression TLR7 [72]. Our systematic review result also confirmed that obesity was associated with death in coronavirus patients. Indeed previously limited scale meta-analysis study [70] had also shown the same findings.

From our systematic review, we found that diabetes, CVDs, COPD, hypertension, and acute kidney injury were the significant risk for COVID-19 mortality. These factors were also reported as the coronavirus risk factor by CDC and WHO. With regard to patients’ COPD status and COVID-19 mortality association, studies [9] have argued that COPD patients with COVID-19 showed higher rates of hospitalization and mortality. This could be due to viral infections in COPD patients increase systemic inflammation with the slow recovery of reported symptoms [80]. In addition to the influence of coronavirus, COPD patients have various comorbidities, some of which are associated with an increased risk of hospitalization [69].

Diabetes also contributes to more severe COVID-19 and higher rates of mortality [81]. Our analysis also showed that mortality among hospitalized COVID-19 patients with diabetes was higher compared to the patients without diabetes. Thus, patients with diabetes and COVID-19 often need invasive ventilation care and need intensive care unit (ICU) as their likelihood of developing Acute Respiratory Distress Syndrome (ARDS) [73]. Another two small systematic reviews, by [67, 73] also suggested that diabetes is a determinant of severity and mortality of COVID-19 patients.

Having a high D-dimer has shown a significantly increased odds of mortality. Previous study [59] had also shown that a high level of D-dimer increases severe infection and risk of mortality. In addition a study in China [17] have shown that rising D-dimer levels during the course of hospitalization are associated with the worst long-term outcomes. Therefore, using D-dimer levels as a surrogate marker for disease severity, especially, in coronavirus patients who cannot get dedicated imaging might be beneficial.

Study limitations

Although this systematic review presented pooled estimate from 42 studies across 13 geographical locations and may be considered broadly representative of the pandemic, our study has a few limitations. First, high heterogeneity could be found. This may relate to large variation in the sample size among studies (98–211,003 patients) and the study designs. Second, the literature on coronavirus continues to accumulate, new information and new papers published each day; therefore, our study cannot be considered as exhaustive. Finally, the sample size of some included studies was very small which might not recognize the possible factors that affects COVID-19 mortality.

Conclusion

Our study indicated a consistent and statistically significant effect of chronic comorbidities, complications, and demographic variables including acute kidney injury, COPD, diabetes, hypertension, CVDs, cancer, increased D-dimer, male gender, older age, current smoker, and
obesity on the fatal outcome of COVID-19. Urgent public health interventions should be carefully tailored and implemented on those susceptible groups to reduce the risk of mortality in patients with COVID-19 and, then, the risk of major complications. An intensive and regular follow-up is required to detect early occurrences of clinical conditions.

Abbreviations
ARDs: Acute respiratory distress syndrome; COVID-19: Coronavirus infection pneumonia 2019; MERS: Middle East respiratory syndrome; pHRR: Pooled hazard-ratio; pOR: Pooled odds-ratio; PRISMA-P: Preferred reporting items for systematic reviews and meta-analyses protocols; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Authors’ information
ZGD is a postdoctoral student and TZ is senior professors at the University of KwaZulu-Natal.

Acknowledgements
We would like to thank the School of Mathematics, Statistics and Computer Science, University of KwaZulu-Natal, South Africa for providing their guidance and support.

Authors’ contributions
ZGD designed the study, extracted and analyzed the data, and wrote the article. TZ contributed to the idea and design of this study, advised on analysis and revised the manuscript. Both authors searched the literature. Both authors read and approved the final manuscript.

Funding
No funding bodies played any role in the design, writing or decision to publish this manuscript.

Availability of data and materials
The dataset used and analyzed during the current study is available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1 School of Mathematics, Statistics and Computer Science, University of KwaZulu-Natal, Durban, South Africa. 2 College of Science, Bahir Dar University, Bahir Dar, Ethiopia.

Received: 10 June 2021 Accepted: 11 August 2021 Published online: 21 August 2021

References
1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R. A novel coronavirus from patients with pneumonia in China, 2019.N. Engl. J. Med. 2020;382:727–733.
2. Peeri NC, Shrestha N, Rahman MS, Zaki R, Du R, Fan G, Liu Y, Hua J, Chen B, Wang Y. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. JAMA. 2020;323(1):126–4.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X. Clinical features of 152 patients including 19 with critical illness who received care in a dedicated COVID-19 hospital in Wuhan, China. Lancet. 2020;395(10223):497–506.
4. Wu Z, McGoogan JM. Characteristics of and important lessons from the SARS, MERS and novel coronavirus disease 2019 (COVID-19) outbreaks in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(15):1329–42.
5. Aqtahini JS, Eydelde T, Alhadari AM, Alhamadi SM, Almehmadi M, Alqasemi AS, Quaderi S, Mandal S, Hurst JR. Prevalence, severity and mortality associated with COVID-20: a rapid systematic review and meta-analysis. PLoS ONE. 2020;15(5):e0233147.
6. Chen M, Fan Y, Wu X, Zhang L, Guo T, Deng K, Cao J, Luo H, He T, Gong Y. Clinical characteristics and risk factors for fatal outcome in patients with COVID-19: a systematic review and meta-analysis. J Med Virol. 2020;92(5):576–582.
7. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. JAMA. 2020;323(15):1329–42.
8. Hutton B, Salanti G, Caldwell CH, Chaimani A, Schmid CH, Ioannidis JP, Grimshaw J, Liberati A,WL. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162(11):777–84.
9. Wells GA, Shea B, O’Connell D, Peterson J, Welch V, Losos M, Tugwell P. Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis. 2009. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.
10. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60.
11. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. JAMA. 2006;295(6):676–80.
12. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(1024):1054–62.
13. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thurlow K, Jansen JP. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162(11):777–84.
14. Wells GA, Shea B, O’Connell D, Peterson J, Welch V, Losos M, Tugwell P. Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis. 2009. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.
15. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60.
16. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. JAMA. 2006;295(6):676–80.
17. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020;395(1024):1054–62.
18. Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, Chen X, Chen S, Yu K, Huang Z. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. J Intensive Care. 2020;8(1):1–11.
19. Xu J, Yang X, Yang L, Zou X, Wang Y, Wu Y, Zhou T, Yuan Y, Qi H, Fu S. Clinical course and predictors of 60-day mortality in 239 critically ill patients with COVID-19: a multicenter retrospective study from Wuhan China. Crit Care. 2020;24(1):1–11.
20. Wang L, He W, Yu X, Hu D, Bao M, Liu H, Zhou J, Jiang H. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on a 4-week follow-up. J Infect. 2020;80:639–645.
21. van Gemert B, Kooistra R, Brouwer J, van der Most PG, Middelkoop E, Jansen PM, Moons KG. COVID-19: a rapid systematic review and meta-analysis. JAMA. 2020;323(15):1329–42.
22. Soares RC, Mattos LR, Raposo LM. Risk factors for hospitalization and mortality due to COVID-19 in Espirito Santo State, Brazil. Am J Trop Med Hyg. 2020;103(3):1184–1190.

23. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020; https://doi.org/10.1001/jamacardio.2020.0950.

24. Shah P, Owens J, Franklin J, Mehta A, Heymann W, Sewell W, Hill J, Barfield K, Doshi R. Demographics, comorbidities and outcomes in hospitalized COVID-19 patients in rural southwest Georgia. Ann Med. 2020;52(7):534–540.

25. Rivera-Izquierdo M, del Carmen V-L, del Alamo JL, Fernández-García MA, Martínez-Díaz S, Tahery-Mahmoud A, Rodríguez-Camacho M, Gámiz-Molina AB, Barba-Gyengo N, Gámiz-Baeza P. Sarcodemo- graphic, clinical and laboratory factors on admission associated with COVID-19 mortality in hospitalized patients: a retrospective observational study. PLoS ONE. 2020;15(6):e023107.

26. Priyank S, Jack Q, James F, Akhtar M, William H, William S, Jennifer H, Krista B, Rajkumar D. Demographics, comorbidities, and outcomes in hospitalized COVID-19 patients in rural Southeast Georgia. Ann Med. 2020;52(5):1791–1356.

27. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and mortality among black patients and white patients with Covid-19. N Engl J Med. 2020;382:2534–43.

28. Pettit NN, Mackenzie EL, Ridgway J, Pursell K, Ash D, Patel B, Pho MT. Obesity is associated with increased risk for mortality among hospitalized patients with COVID-19. Obesity. 2020;28(10):1806–10.

29. Petrelli CM, Jones SA, Yang J, Rajagopalan H, O’Donnell L, Chernyak Y, Tobin KA, Cefkoflo RJ, Francois F, Horwitz L. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City. prospective cohort study. BMJ. 2020;369:m1966.

30. Parra-Bracamonte G, Lopez-Villalobos N, Parra-Bracamonte F. Clinical characteristics and risk factors for mortality of patients with COVID-19 in a large dataset from Mexico. Ann Epidemiol. 2020;52:93–8.

31. Palacioslos M, Kokkinidis D, Li W, Karamanis D, Ognibene J, Arora S, Palaiodimos L, Kokkinidis D, Li W, Karamanis D, Ognibene J, Arora S. Clinical characteristics and risk factors for mortality in patients with COVID-19 in New York City. J Gen Intern Med. 2021;36:17–26.

32. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular characteristics and risk factors for mortality among hospitalized COVID-19 patients in Rural Southwest Georgia. JAMA Cardiol. 2020;7:86–96.

33. Li X, Xu S, Wang W, Zhao K, Tong Y, Shi J, Zhou M, Wu B, Yang Z. Obesity is associated with increased risk for mortality among hospitalized patients with COVID-19 in New York City. N Engl J Med. 2020;382(25):e102. https://doi.org/10.1056/NEJMoa2007621.

34. Lim J-H, Park S-H, Jo H, Jung H-Y, Choi J-Y, Kim C-D, Lee Y-H, Petrilli CM, Jones SA, Yang J, Rajagopalan H, O’Donnell L, Chernyak Y, Tobin KA, Cefkoflo RJ, Francois F, Horwitz L. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City. prospective cohort study. BMJ. 2020;369:m1966.

35. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and mortality among black patients and white patients with Covid-19. N Engl J Med. 2020;382:2534–43.

36. Pettit NN, Mackenzie EL, Ridgway J, Pursell K, Ash D, Patel B, Pho MT. Obesity is associated with increased risk for mortality among hospitalized patients with COVID-19. Obesity. 2020;28(10):1806–10.

37. Petrelli CM, Jones SA, Yang J, Rajagopalan H, O’Donnell L, Chernyak Y, Tobin KA, Cefkoflo RJ, Francois F, Horwitz L. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City. prospective cohort study. BMJ. 2020;369:m1966.

38. Soares RC, Mattos LR, Raposo LM. Risk factors for hospitalization and mortality due to COVID-19 in Espirito Santo State, Brazil. Am J Trop Med Hyg. 2020;103(3):1184–1190.

39. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020; https://doi.org/10.1001/jamacardio.2020.0950.

40. Shah P, Owens J, Franklin J, Mehta A, Heymann W, Sewell W, Hill J, Barfield K, Doshi R. Demographics, comorbidities and outcomes in hospitalized COVID-19 patients in rural southwest Georgia. Ann Med. 2020;52(7):534–540.

41. Rivera-Izquierdo M, del Carmen V-L, del Alamo JL, Fernández-García MA, Martínez-Díaz S, Tahery-Mahmoud A, Rodríguez-Camacho M, Gámiz-Molina AB, Barba-Gyengo N, Gámiz-Baeza P. Sarcodemo- graphic, clinical and laboratory factors on admission associated with COVID-19 mortality in hospitalized patients: a retrospective observational study. PLoS ONE. 2020;15(6):e023107.

42. Priyank S, Jack Q, James F, Akhtar M, William H, William S, Jennifer H, Krista B, Rajkumar D. Demographics, comorbidities, and outcomes in hospitalized COVID-19 patients in rural Southeast Georgia. Ann Med. 2020;52(5):1791–1356.

43. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and mortality among black patients and white patients with Covid-19. N Engl J Med. 2020;382:2534–43.

44. Pettit NN, Mackenzie EL, Ridgway J, Pursell K, Ash D, Patel B, Pho MT. Obesity is associated with increased risk for mortality among hospitalized patients with COVID-19. Obesity. 2020;28(10):1806–10.

45. Petrelli CM, Jones SA, Yang J, Rajagopalan H, O’Donnell L, Chernyak Y, Tobin KA, Cefkoflo RJ, Francois F, Horwitz L. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City. prospective cohort study. BMJ. 2020;369:m1966.

46. Parra-Bracamonte G, Lopez-Villalobos N, Parra-Bracamonte F. Clinical characteristics and risk factors for mortality of patients with COVID-19 in a large dataset from Mexico. Ann Epidemiol. 2020;52:93–8.

47. Palacioslos M, Kokkinidis D, Li W, Karamanis D, Ognibene J, Arora S, Palaiodimos L, Kokkinidis D, Li W, Karamanis D, Ognibene J, Arora S. Clinical characteristics and risk factors for mortality in patients with COVID-19 in New York City. J Gen Intern Med. 2021;36:17–26.

48. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular characteristics and risk factors for mortality in patients with COVID-19 in New York City. N Engl J Med. 2020;382(25):e102. https://doi.org/10.1056/NEJMoa2007621.

49. Lim J-H, Park S-H, Jeon Y, Cho J-H, Jung H-Y, Choi J-Y, Kim C-D, Lee Y-H, See O, Lee J. Fatal outcomes of COVID-19 in patients with severe acute kidney injury. J Clin Med. 2020;9(6):1718.

50. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, Shi J, Zhou M, Wu B, Yang Z. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020;146(1):110–8.

51. Lee LY, Cazier JB, Starkey T, Turnbull C, Team UCCMP, Kerr R, Middleton G. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. The Lancet. 2020;395(10241):1195–26.

52. Lee JY, Kim HA, Huh K, Hyun M, Rhee J-Y, Jiang S, Kim J-Y, Peck KR, Chang H-H. Risk factors for mortality and respiratory support in elderly patients hospitalized with COVID-19 in Korea. J Korean Med Sci. 2020;35:e223.

53. Kuderer NM, Choueiri TK, Shah DP, Shyr Y, Rubinstein SM, Rivera DR, Shete S, Taghian A, de Lima Lopes Jr G. Clinical impact of COVID-19 on patients with cancer (CCCI9): a cohort study. Lancet. 2020;395:1907–18.

54. Klang E, Kassim G, Soffer S, Freeman R, Levin MA, Reich DL. Morbid obesity as an independent risk factor for COVID-19 mortality in hospitalized patients younger than 50 years. 2020;28(9):1595–9.

55. Hernández-Gálvez ME, González-Block MA, Romo-Duenas DK, Lima-Morales R, Hernández-Vicente IA, Lumberas-Guzmán M, Méndez-Hernández P. Increased risk of hospitalization and death in patients with COVID-19 and pre-existing noncommunicable diseases and modifiable risk factors. Arch Med Res. 2020;51(7):683–9.
and chronic obstructive pulmonary disease patients. Clin Infect Dis. 2018;66(1):45–53.
61. Rojas-Osornio SA, Cruz-Hernández TR, Drago-Serrano ME, Campos-Rodríguez R. Immunity to influenza: impact of obesity. Obes Res Clin Pract. 2019;13(5):419–29.
62. Opal SM, Girard TD, Ely EW. The immunopathogenesis of sepsis in elderly patients. Clin Infect Dis. 2005;41(Supplement_7):S504–12.
63. Kumar A, Arora A, Sharma P, Anikhindii SA, Bansal N, Singla V, Khare S, Sriivastava A. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. Diabet Metab Syndr. 2020;14(4):535–545.
64. Karanasos A, Aznaouridis K, Latsios G, Synetos A, Plitaria S, Tousoulis D, Toutouzas K. Impact of smoking status on disease severity and mortality of hospitalized patients with COVID-19 infection: a systematic review and meta-analysis. Nicotine Tobacco Res. 2020;22(9):1657–9.
65. Jaillon S, Berthenet K, Garlanda C. Sexual dimorphism in innate immunity. Clin Rev Allergy Immunol. 2019;56(3):308–21.
66. Hong K-H, Choi J-H, Hong S-H, Lee J, Kwon J-S, Kim S-M, Park SY, Rhee J-Y, Kim B-N, Choi HJ. Predictors of mortality in Middle East respiratory syndrome (MERS). Thorax. 2018;73(3):286–9.
67. Fadini G, Morieri M, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. J Endocrinol Invest. 2020;43(6):867–9.
68. Choi KW, Chau TN, Tsang O, Tsao E, Chiu MC, Tong WJ, Lee PO, Ng TK, Ng WF, Lee KC. Outcomes and prognostic factors in 267 patients with severe acute respiratory syndrome in Hong Kong. Ann Intern Med. 2003;139(9):715–23.
69. Hurst JR, Skolnik N, Hansen GJ, Anzueto A, Donaldson GC, Dransfield MT, Varghese P. Understanding the impact of chronic obstructive pulmonary disease exacerbations on patient health and quality of life. Eur J Intern Med. 2020;73:1–6.
70. Tamara A, Tahapary DL. Obesity as a predictor for a poor prognosis of COVID-19: A systematic review. Diabetes Metab Syndr. 2020;14(4):655–659.
71. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, Aaron JG, Claassen J, Rabbani LE, Hastie J. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet. 2020;395(10239):1763–70.
72. Parohan M, Yaghoubi S, Seraji A, Javanbakht MH, Sarraf P, Djali M. Risk factors for mortality in patients with Coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of observational studies. The Aging Male. 2020;23(5):1416–24.