Prognostic factors for mortality, intensive care unit and hospital admission due to SARS-CoV-2: a systematic review and meta-analysis of cohort studies in Europe

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There is a strong association between specific prognostic factors and mortality and hospital admission due to SARS-CoV-2, including, but not limited to, diabetes, cardiovascular diseases and respiratory diseases. https://bit.ly/3Qo4zCc

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Abstract

Background As mortality from coronavirus disease 2019 (COVID-19) is strongly age-dependent, we aimed to identify population subgroups at an elevated risk for adverse outcomes from COVID-19 using age-/gender-adjusted data from European cohort studies with the aim to identify populations that could potentially benefit from booster vaccinations.

Methods We performed a systematic literature review and meta-analysis to investigate the role of underlying medical conditions as prognostic factors for adverse outcomes due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), including death, hospitalisation, intensive care unit (ICU) admission and mechanical ventilation within three separate settings (community, hospital and ICU). Cohort studies that reported at least age and gender-adjusted data from Europe were identified through a search of peer-reviewed articles published until 11 June 2021 in Ovid Medline and Embase. Results are presented as odds ratios with 95% confidence intervals and absolute risk differences in deaths per 1000 COVID-19 patients.

Findings We included 88 cohort studies with age-/gender-adjusted data from 6 653 207 SARS-CoV-2 patients from Europe. Hospital-based mortality was associated with high and moderate certainty evidence for solid organ tumours, diabetes mellitus, renal disease, arrhythmia, ischemic heart disease, liver disease and obesity, while a higher risk, albeit with low certainty, was noted for chronic obstructive pulmonary disease and heart failure. Community-based mortality was associated with a history of heart failure, stroke, diabetes and end-stage renal disease. Evidence of high/moderate certainty revealed a strong association between hospitalisation for COVID-19 and solid organ transplant recipients, sleep apnoea, diabetes, stroke and liver disease.

Interpretation The results confirmed the strong association between specific prognostic factors and mortality and hospital admission. Prioritisation of booster vaccinations and the implementation of nonpharmaceutical protective measures for these populations may contribute to a reduction in COVID-19 mortality, ICU and hospital admissions.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has led to detrimental consequences for society, the global economy and public health. Healthcare systems worldwide continue to face high pressure, particularly at peaks of transmission waves. After a period of decrease during the European summer months of 2021, increases in the number of cases and hospital and intensive care unit (ICU) admissions have been noted from October 2021 in most of the European Union and European Economic Area (EU/EEA) countries [1]. According to the European Centre for Disease Prevention and Control (ECDC)'s most recent risk assessment, this rise was mainly attributed to the newly emerging variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), such as the Delta variant (B.1.617.2) and the Omicron variant (B.1.1.529), the loosening of nonpharmaceutical interventions (NPIs) across Europe and inadequate vaccination coverage [2].

In an effort to stratify patients with SARS-CoV-2 for better management of economic and human resources, particular attention has been paid to the determination of risk factors that predispose to adverse outcomes related to COVID-19, including hospitalisation, ICU admission, the need for ventilatory support or death. Consistent evidence demonstrates a high risk of severe COVID-19 manifestations in older individuals, especially in combination with pre-existing medical conditions [3–5]. Population-level data have indicated that older COVID-19 patients with comorbidities such as chronic cardiac, nonasthmatic chronic pulmonary, chronic kidney and liver diseases, and obesity have higher mortality in hospitals [6–8]. Although the European Surveillance System has noted through the use of population data that COVID-19 patients with cardiac disorders (25.7%), diabetes (15.5%) and cancers (9.9%) have the highest case-fatality rates in the European population [9], and while previous systematic reviews have separately assessed several clinical indicators or comorbidities, they lack age-/gender-adjusted analyses and stratification by patient setting [4].

As mortality from COVID-19 is strongly age-dependent, a meta-analysis of pooled age-adjusted estimates from available cohort studies is needed to determine which comorbidities should classify patients into high-risk groups for adverse COVID-19 outcomes. Additionally, as new variants of SARS-CoV-2 emerge, most updated scientific evidence should be regularly assessed regarding the risk factors for adverse COVID-19 outcomes. For example, the newest variant called Omicron (B1.1.529), which was declared as a variant of concern by the World Health Organisation (WHO) on 26 November 2021 [10], has caused severe pneumonia in young patients even without profound risk factors [11]. Such evidence would be of interest to clinicians to better manage patient flow and to policymakers when planning forthcoming public health measures, such as booster vaccination strategies in coming phases of the pandemic.

Methods

The systematic review as conducted adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) [12] and MOOSE (Meta-analyses Of Observational Studies in Epidemiology) guidelines [13]. The protocol of this systematic review was pre-reviewed by the ECDC. The protocol was not pre-registered in any database for systematic reviews.

Only cohort studies conducted in Europe, including EU/EEA countries, the United Kingdom (UK) and Switzerland were considered eligible provided 1) they evaluated patients with clinically diagnosed or laboratory-confirmed COVID-19 in one of three settings (community, hospital or ICU) and 2) they assessed the associations between underlying clinical conditions (as risk factors) and primary adverse outcomes of COVID-19. All underlying clinical conditions (risk factors) that were described in the original studies were considered acceptable for data extraction as long as the results were at least age- and gender-adjusted. All other study designs (*i.e.* case control, cross-sectional), were excluded, as were cohorts that provided only unadjusted data.

The primary outcomes of our meta-analyses were mortality, hospital admission and ICU admission. Supplementary outcomes included, where available, the use of mechanical ventilatory support and a composite outcome comprising admission to the ICU and/or death and/or hospice care (*e.g.* "death or ICU admission"). The latter secondary outcome was considered crucial to account for the bias introduced by excluding patients from higher levels of care due to their poor baseline status or severe comorbidities.

Relevant peer-reviewed studies published in English were identified within Medline (Ovid) and Embase (Ovid) until 11 June 2021. Subject headings relating to COVID-19 and epidemiological study design terms were used to develop a comprehensive search strategy, presented in Appendix 1. Reference lists of all included studies and identified reviews were also screened to identify additional relevant studies. Full texts

of potentially eligible studies were evaluated independently by two reviewers. Disagreements or uncertainties in screening stages were resolved through discussion and consensus.

An *ad hoc* designed structured form was used for the adjusted data from each eligible study, including details on the study design, baseline characteristics of the participants, clinical conditions (risk factors) and outcome data (mortality, hospitalisation, ICU admission). For accuracy, each study's data were extracted by one reviewer, with each study cross-checked by a second. Adequate information was extracted to allow us to identify overlapping populations across studies. In the case of overlapping populations, we prioritised including data from the study with the larger population and a more rigorously described methodology.

The methodological quality of each included study was evaluated independently by two reviewers using the Joanna Briggs Institute (JBI) standardised critical appraisal tool for the appropriate design [8]. Disagreements were resolved with discussion and, when necessary, adjudication by a third reviewer.

The certainty of the evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used for evaluating the certainty in the body of evidence for each meta-analysis [14]. In line with GRADE recommendations for the assessment of evidence about prognostic factors, we initially ascribed high certainty for all our findings which were subsequently rated down in cases of study limitations of the included studies, inconsistency, indirectness or imprecision of the results, or evidence of publication bias. Moreover, certainty was rated up in cases of large observed effects. Results that were of high or moderate certainty are primarily reported in the text of the current article.

Statistical analysis

In anticipation of significant clinical and methodological heterogeneity in the meta-analyses, we fitted logistic regression models with random effects. All outcome data were adjusted at least for gender and age. All variables analysed were dichotomous and analysed as odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs). Heterogeneity was quantified using the I^2 statistics. We considered values above 75% to represent considerable heterogeneity. To facilitate interpretability of the results and in line with recommendations by GRADE [14], we also present the absolute risk differences (RDs) per 1000 COVID-19 patients with corresponding 95% CI. The median prevalence of the evaluated risk factors and the median incidence rate of each adverse outcome in each recruitment setting were used for calculating the absolute RDs.

Results

We included 88 studies, involving 6 653 207 cases with COVID-19 in the review (PRISMA flowchart: figure 1). Recruitment dates ranged from 1 January 2020 to 30 April 2021, but were primarily based in 2020. There were 69 cohort studies that assessed 6 029 126 patients in the hospital setting [15–83], 13 cohort studies involving 621 792 patients in the community setting – of which 10 were based solely in the community [84–93] while three combined community/hospital recruitment [94–96], and six cohort studies involving 2289 patients based in the ICU setting [97–102]. Details on the characteristics of the included cohort studies are presented in Appendix 2, while the assessment of the risk of bias according to the JBI critical appraisal tool is provided in Appendix 3.

As per our inclusion criteria, all cohort studies were based in Europe and included 23 studies from Spain [16, 18, 19, 24, 30, 31, 34, 35, 37, 52, 56, 59–61, 66, 69, 72, 82, 91, 94, 98, 99, 103], 22 studies from Italy [15, 21, 23, 25, 27, 32, 40, 41, 47, 49, 50, 57, 58, 63, 64, 70, 73, 79, 81, 92, 93, 95], 15 studies from France [22, 26, 29, 33, 42, 43, 45, 55, 62, 65, 67, 76, 78, 88, 101], 10 studies from the UK [28, 36, 46, 51, 54, 68, 74, 77, 89, 100], four included patients from more than one country [71, 75, 90, 96], three from Germany [48, 53, 80], two studies from Sweden [38, 102], two from Denmark [44, 85] and one study each from Belgium [83], Finland [5], the Netherlands [20], Norway [87] and Poland [39]. The diagnosis of COVID-19 was made mainly with a PCR test, except for in five studies in which the diagnosis was made with the International Classification of Diseases [104 22, 26, 29, 44, 86].

Underlying medical conditions as prognostic factors of mortality due to COVID-19

While all meta-analyses findings are presented with both adjusted OR (aOR) and absolute RDs in figures 2a–b, below, we primarily present key results supported by evidence of moderate or high certainty as assessed using the GRADE approach.

The presence of any cardiovascular disease posed an increased risk for mortality in the hospital setting (51 (95% CI 17–85) more deaths per 1000 cases; high certainty). Additionally, stroke (35 (95% CI 3–75) more deaths per 1000 cases; high certainty) and heart failure (57 (95% CI 13–144) more deaths per 1000 cases;

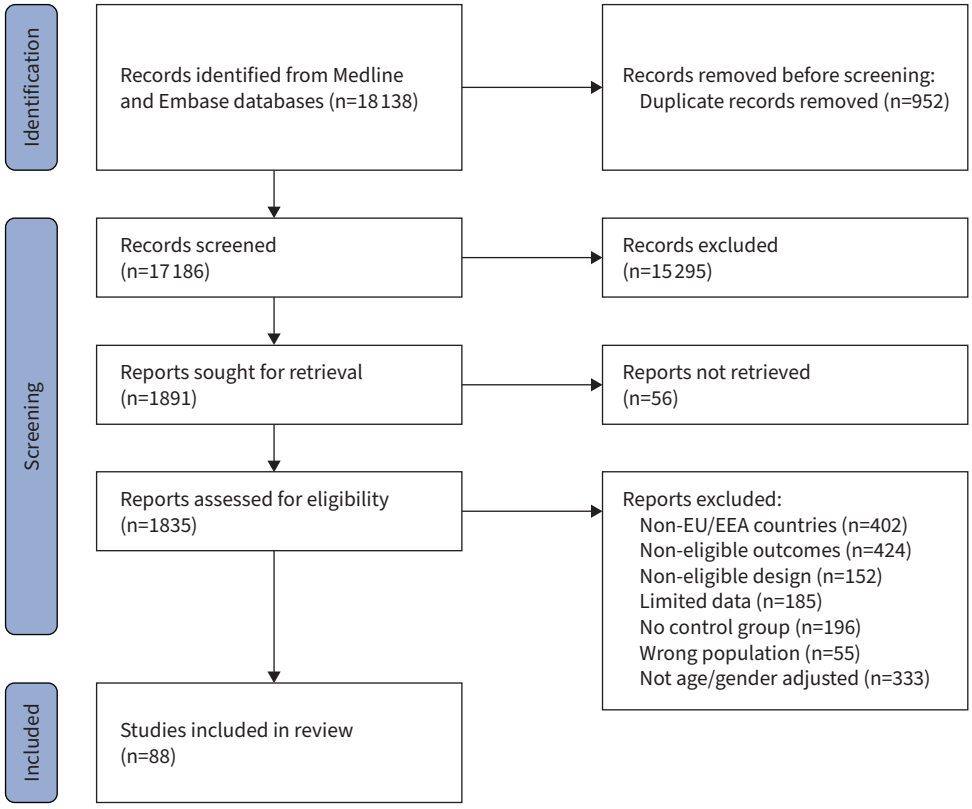


FIGURE 1 PRISMA flowchart of the included studies.

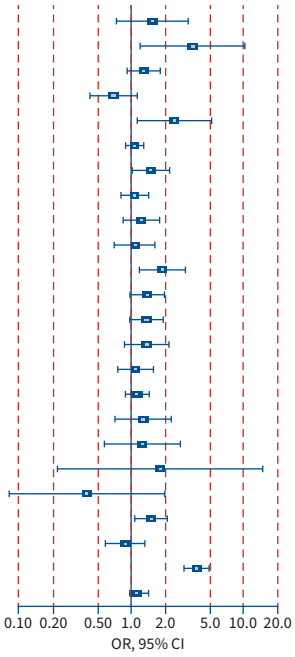
moderate certainty) were associated with increased mortality risk in the community setting, while ischaemic heart disease (IHD) was estimated to increase the risk of death in hospitalised patients with COVID-19 by 187 (95% CI 11–385) more deaths per 1000 cases (moderate certainty). Diabetes mellitus was associated with increased mortality in the hospital setting as 57 (95% CI 31–84) (high certainty) additional deaths were observed for every 1000 patients recruited with COVID-19 and diabetes mellitus. Arrythmia was associated with increased mortality in the hospital setting (174 (95% CI 28–338); moderate certainty). A history of solid organ transplant receipt was associated with increased mortality in the community setting (163 (95% CI 124–206) more deaths per 1000 cases; high certainty). Patients with neurological disease were also at an elevated risk of death within both the hospital (133 (95% CI 17–264) more deaths per 1000 cases; moderate certainty) and the community setting (34 (95% CI 7–67) more deaths per 1000 cases; moderate certainty). Similarly, COVID-19 patients with any respiratory disease were found to have increased mortality risk in the community (142 (95% CI 16–339) more deaths per 1000 cases; moderate certainty) and in the ICU (94 (95% CI 13–176) more deaths per 1000 cases; moderate certainty) setting.

Other factors associated with an increased mortality in the hospital setting were renal disease (91 (95% CI 25–163); moderate certainty); dementia (99 (95% CI 4–209); moderate certainty); cancer (121 (95% CI 78–166); high certainty); liver disease (239 (95% CI 53–441); moderate certainty); and male gender (68 (95% CI 50–86); high certainty). Male gender was found to be associated with increased death also in the ICU setting (96 (95% CI 22–166); moderate certainty). Data regarding the presence of other comorbid diseases with COVID-19 mortality were less consistent or of lower certainty.

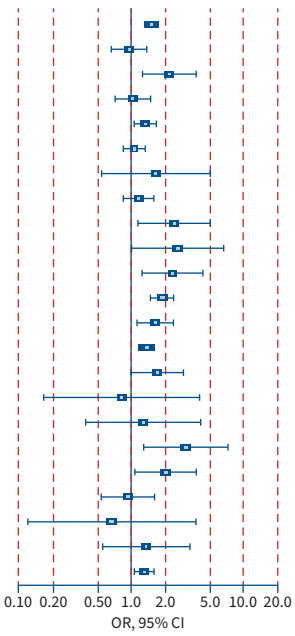
Hospital and ICU admission

Figure 3 presents a forest plot that summarises the available evidence presented as aOR and absolute RDs regarding the association between COVID-19 and hospital admission within the community setting. Increased hospitalisation per 1000 COVID-19 patients was noted for the history of solid organ transplant (320; 95% CI 276–360) and sleep apnoea (262; 95% CI 5–457), supported by evidence of high certainty. Moreover, other prognostic factors were associated with hospital admission with evidence of moderate certainty and included any cardiovascular disease (156; 95% CI 67–242), heart failure (291; 95% CI 190–379), any respiratory disease (278; 95% CI 157–380), diabetes (129; 95% CI 73–185) and male gender

Prognostic factor	N (n)	Main analysis OR (95% CI)	I^2	Absolute risk difference (95% CI)
Male gender	2 (1988)	1.548 (0.75–3.193)	99.96	32 more per 1000 (–21–80)
Any respiratory disease	1 (180)	3.5 (1.219–10.053)	0	142 more per 1000 (16–339)
COPD	4 (17 070)	1.28 (0.914–1.793)	24.22	20 more per 1000 (–6–53)
Asthma	3 (5950)	0.689 (0.422–1.127)	14.5	24 fewer per 1000 (–48–9)
Any cardiovascular disease	2 (1718)	2.404 (1.125–5.138)	65.58	80 more per 1000 (9–168)
Hypertension	3 (15 532)	1.057 (0.884–1.264)	0	4 more per 1000 (–9–17)
Stroke	2 (4412)	1.505 (1.044–2.168)	4.65	35 more per 1000 (3–75)
Dyslipidaemia	2 (4412)	1.06 (0.804–1.398)	28.73	4 more per 1000 (–15–26)
Arrhythmia	2 (4412)	1.219 (0.844–1.761)	50.31	15 more per 1000 (–12–50)
IHD	2 (4412)	1.059 (0.709–1.58)	0	4 more per 1000 (–22–39)
Heart failure	3 (15 532)	1.882 (1.186–2.988)	41.37	57 more per 1000 (13–114)
Cancer	4 (15 712)	1.367 (0.966–1.935)	0	26 more per 1000 (–2–61)
Renal	4 (4712)	1.325 (0.918–1.913)	38.79	23 more per 1000 (–6–60)
Diabetes	4 (6130)	1.363 (0.871–2.131)	82.03	24 more per 1000 (–10–66)
Endocrine	4 (8824)	1.079 (0.767–1.52)	29.31	6 more per 1000 (–18–35)
Dementia	2 (4412)	1.135 (0.904–1.424)	0	10 more per 1000 (–7–29)
Gastrointestinal	2 (4412)	1.267 (0.73–2.202)	0	19 more per 1000 (–20–79)
Haematological	2 (3638)	1.248 (0.576–2.705)	80.95	18 more per 1000 (–32–109)
HIV	1 (180)	1.8 (0.219–14.788)	0	54 more per 1000 (–62–449)
Liver disease	1 (180)	0.4 (0.082–1.96)	0	46 fewer per 1000 (–73–64)
Neurological	3 (4592)	1.49 (1.093–2.031)	0	34 more per 1000 (7–67)
Rheumatological or autoimmune	5 (19 944)	0.867 (0.597–1.26)	66.3	10 fewer per 1000 (–31–18)
Solid organ transplant	1 (450)	3.83 (3.027–4.846)	0	163 more per 1000 (124–206)
Obesity	2 (4412)	1.138 (0.925–1.399)	18.06	9 more per 1000 (–6–25)



Prognostic factor	N (n)	Main analysis OR (95% CI)	I^2	Absolute risk difference (95% CI)	Grade
Male gender	16 (271 824)	1.524 (1.358–1.71)	24.36	68 more per 1000 (50–86)	High
Any respiratory disease	3 (2239)	0.98 (0.71–1.371)	0	3 fewer per 1000 (–55–55)	Low
COPD	5 (3288)	2.209 (1.313–3.716)	64.47	154 more per 1000 (48–273)	Low
Sleep apnoea	1 (5795)	1.04 (0.743–1.456)	0	7 more per 1000 (–46–68)	Low
Any cardiovascular disease	9 (4920)	1.344 (1.109–1.63)	1.75	51 more per 1000 (17–85)	High
Hypertension	12 (270 801)	1.07 (0.877–1.307)	63.33	11 more per 1000 (–22–44)	Very low
Stroke	3 (3014)	1.678 (0.562–5.01)	80.41	96 more per 1000 (–82–344)	Low
Dyslipidaemia	4 (7183)	1.169 (0.871–1.569)	19.03	27 more per 1000 (–22–81)	Moderate
Arrhythmia	1 (637)	2.44 (1.177–5.058)	0	174 more per 1000 (28–338)	Moderate
IHD	2 (1401)	2.627 (1.065–6.476)	52.43	187 more per 1000 (11–385)	Moderate
Heart failure	5 (8426)	2.358 (1.288–4.315)	69.42	166 more per 1000 (44–302)	Low
Cancer	9 (98 563)	1.898 (1.54–2.34)	42.94	121 more per 1000 (78–166)	High
Renal	9 (10 933)	1.652 (1.157–2.36)	67.97	91 more per 1000 (25–163)	Moderate
Diabetes	12 (12 038)	1.395 (1.204–1.617)	17.33	57 more per 1000 (31–84)	High
Dementia	3 (700)	1.711 (1.022–2.867)	0	99 more per 1000 (4–209)	Moderate
HIV	1 (126)	0.83 (0.171–4.026)	0	29 fewer per 1000 (–169–304)	Low
Immunosuppresion	1 (576)	1.295 (0.405–4.139)	0	46 more per 1000 (–118–299)	Moderate
Liver disease	5 (260 469)	3.09 (1.34–7.124)	79.24	239 more per 1000 (53–441)	Moderate
Neurological	2 (667)	2.033 (1.109–3.279)	11.01	133 more per 1000 (17–264)	Moderate
Rheumatological or autoimmune	3 (3118)	0.937 (0.549–1.597)	46.84	11 fewer per 1000 (–84–87)	Moderate
Solid organ transplant	2 (1638)	0.677 (0.122–3.746)	81.87	58 fewer per 1000 (–183–285)	Very low
VTE	1 (340)	1.38 (0.57–3.34)	0	58 more per 1000 (–80–255)	Low
Obesity	11 (266 865)	1.329 (1.113–1.587)	77.3	48 more per 1000 (18–79)	Low



Prognostic factor	N (n)	Main analysis OR (95% CI)	I^2	Absolute risk difference (95% CI)	Grade
Male gender	2 (1637)	1.547 (1.103–2.168)	0	96 more per 1000 (22–166)	Moderate
Any respiratory disease	1 (1563)	1.5 (1.061–2.121)	0	94 more per 1000 (13–176)	Moderate
Any cardiovascular disease	3 (1720)	1.727 (0.55–5.429)	58.12	129 more per 1000 (–123–399)	Very low
Hypertension	2 (1637)	0.897 (0.663–1.213)	0	25 fewer per 1000 (–92–43)	Low
Cancer	1 (74)	1.16 (0.059–22.76)	0	34 more per 1000 (–334–613)	Low
Renal	1 (1563)	0.7 (0.361–1.356)	0	76 fewer per 1000 (–188–71)	Low
Diabetes	2 (1637)	0.989 (0.704–1.39)	0	3 fewer per 1000 (–76–76)	Low
Obesity	3 (364)	1.677 (0.938–2.999)	7.49	119 more per 1000 (–14–254)	Low

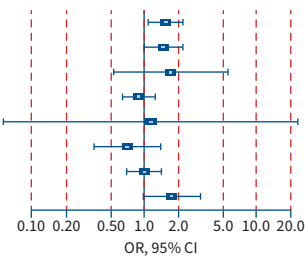


FIGURE 2 Association between prognostic factors and mortality among coronavirus disease 2019 (COVID-19) cases within a) community, b) hospital and c) intensive care unit (ICU) settings. Odds ratios (ORs) (95% confidence intervals (CIs)), I^2 test for heterogeneity, absolute risk differences (95% CIs) and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment are presented. COPD: chronic obstructive pulmonary disease; IHD: ischaemic heart disease; N (n): number of studies (number of population); VTE: venous thromboembolism

Prognostic factor	N (n)	Main analysis OR (95% CI)	I^2	Absolute risk difference (95% CI)	Grade
Male gender	1 (1603)	1.76 (1.395–2.221)	0	137 more per 1000 (81–192)	Moderate
Any respiratory disease	1 (1250)	3.17 (1.888–5.323)	0	278 more per 1000 (157–380)	Moderate
COPD	2 (2853)	3.181 (1.041–9.722)	80.82	279 more per 1000 (10–470)	Low
Sleep apnoea	1 (445)	2.93 (1.022–8.403)	0	262 more per 1000 (5–457)	High
Any cardiovascular disease	1 (1603)	1.88 (1.315–2.689)	0	156 more per 1000 (67–242)	Moderate
Hypertension	3 (13 973)	2.139 (0.896–5.106)	86.08	185 more per 1000 (–27–383)	Low
Stroke	1 (11 120)	1.54 (0.06–39.639)	0	107 more per 1000 (–396–576)	Low
IHD	1 (11 120)	2.89 (0.208–40.119)	0	258 more per 1000 (–299–582)	Low
Heart failure	1 (1250)	3.35 (2.159–5.198)	0	291 more per 1000 (190–379)	Moderate
Cancer	2 (12 723)	1.342 (0.89–2.025)	0	73 more per 1000 (–28–175)	Moderate
Renal	2 (2853)	2.397 (1.124–5.112)	80.29	215 more per 1000 (29–374)	Low
Diabetes	2 (2853)	1.686 (1.344–2.116)	0	129 more per 1000 (73–185)	Moderate
ACEs	1 (1603)	0.7 (0.437–1.122)	0	84 fewer per 1000 (–182–28)	Low
ARBs	1 (1603)	0.91 (0.562–1.474)	0	23 fewer per 1000 (–132–96)	Low
ACEs or ARBs	1 (1603)	0.58 (0.337–1)	0		Moderate
Gastrointestinal	1 (11 120)	2.21 (0.231–21.139)	0	196 more per 1000 (–278–526)	Low
Rheumatological or autoimmune	1 (11 120)	7.37 (0.74–73.354)	0	427 more per 1000 (–71–574)	Low
Solid organ transplant	1 (450)	3.9 (3.152–4.826)	0	320 more per 1000 (276–360)	High

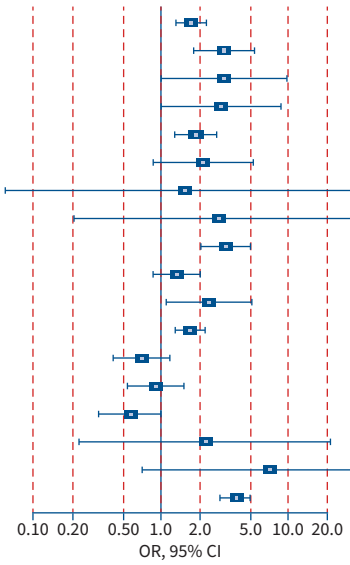


FIGURE 3 Association between prognostic factors and hospital admission among coronavirus disease 2019 (COVID-19) within the community setting. Odds ratios (ORs) (95% confidence intervals (CIs)), I^2 test for heterogeneity, absolute risk differences (95% CIs) and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment are presented for all studies. ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; COPD: chronic obstructive pulmonary disease; IHD: ischaemic heart disease; N (n): number of studies (number of population).

(137; 95% CI 81–192). Figure 4 presents the available evidence of the association between prognostic factors and ICU admission within the hospital setting due to COVID-19. Supported by evidence of moderate certainty, the presence of asthma and neurological diseases was significantly associated with ICU admission, other factors were supported by evidence of lower certainty or indicated nonstatistically significant results.

Prognostic factor	N (n)	Main analysis OR (95% CI)	I^2	Absolute risk difference (95% CI)	Grade
Male gender	5 (7568)	1.463 (1.109–1.929)	31.95	82 more per 1000 (23–140)	Moderate
Any respiratory disease	2 (81 174)	0.877 (0.617–1.247)	83.23	28 fewer per 1000 (–99–49)	Very low
COPD	2 (75 638)	0.917 (0.367–2.288)	65.75	19 fewer per 1000 (–181–196)	Low
Asthma	3 (151 032)	1.178 (1.099–1.262)	0	37 more per 1000 (21–52)	Moderate
Any cardiovascular disease	3 (7244)	0.958 (0.602–1.524)	48.46	9 fewer per 1000 (–106–94)	Moderate
Hypertension	4 (2190)	1.278 (0.842–1.938)	19.97	53 more per 1000 (–38–141)	Moderate
Stroke	2 (1588)	0.639 (0.23–1.773)	0	91 fewer per 1000 (–237–134)	Moderate
Dyslipidaemia	1 (175)	1.58 (0.7–3.568)	0	105 more per 1000 (–74–300)	Low
Cancer	2 (6138)	1.116 (0.799–1.557)	0	24 more per 1000 (–47–102)	Low
Renal	3 (1700)	1.617 (0.581–4.503)	74.15	110 more per 1000 (–110–353)	Low
Diabetes	5 (8259)	1.138 (0.816–1.585)	83.19	28 more per 1000 (–44–103)	Very low
HIV	1 (475 992)	1.22 (0.798–1.865)	0	45 more per 1000 (–47–148)	Moderate
Neurological	1 (5711)	2.67 (2.06–3.46)	0	232 more per 1000 (169–294)	Moderate
Rheumatological or autoimmune	1 (175)	0.25 (0.1–0.622)	0	224 fewer per 1000 (–292–95)	Moderate
Solid organ transplant	1 (212)	0.52 (0.1–2.717)	0	125 fewer per 1000 (–284–241)	Moderate
Obesity	8 (3752)	2.985 (1.879–4.742)	90.61	244 more per 1000 (141–344)	Very low

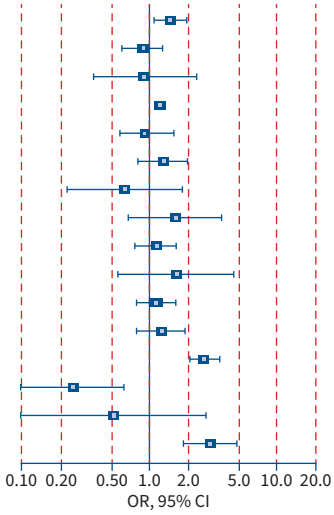


FIGURE 4 Association between prognostic factors and intensive care unit (ICU) admission among coronavirus disease 2019 (COVID-19) cases within the hospital setting. Odds ratios (ORs) (95% confidence intervals (CIs)), I^2 test for heterogeneity, absolute risk differences (95% CIs) and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment are presented for all studies. COPD: chronic obstructive pulmonary disease; N (n): number of studies (number of population).

Composite outcome of death or ICU admission

As a supplementary analysis, we assessed the prognostic factors related to the composite adverse outcome of combined death and/or ICU admission in Appendix 4 for community (Appendix 4a) and hospital settings (Appendix 4b). Among hospitalised patients, the presence of chronic obstructive pulmonary disease (COPD) (252; 95% CI 115–383); dyslipidaemia (95; 95% CI 4–190); hypertension (91; 95% CI 27–153); diabetes (71; 95% CI 47–95) and any cardiovascular disease (76; 95% CI 1–153) was associated with this composite outcome supported by evidence of high certainty. Moreover, obesity (143; 95% CI 94–1920, heart failure (141; 95% CI 39–246) and male gender (144; 95% CI 98–188) were significantly associated with this composite outcome in the hospital setting, supported by evidence of moderate certainty**.** Diabetes (33; 95% CI 4–66) and male gender (33; 95% CI 12–54) were also estimated to increase the risk for ICU admission or death in the community setting with evidence of moderate certainty.

Mechanical ventilation

Appendix 5 presents the assessment of the need for mechanical ventilation, as a secondary outcome, for both the hospital setting (Appendix 5a) and the ICU setting (Appendix 5b). Obesity was associated with an increased need for mechanical ventilation in both the hospital (169; 95% CI 162–176; high certainty) and ICU setting (128; 95% CI 67–176; low certainty). Moreover, data of high certainty indicated an increased risk for mechanical ventilation in hospitalised COVID-19 patients with asthma (18; 95% CI 2–35), while male gender was associated with a higher odds of mechanical ventilation need in both hospital (108; 95% CI 48–164; high certainty) and ICU settings (172; 95% CI 3–321; moderate certainty).

Discussion

Based on quantitative age- and gender-adjusted data extracted from 88 cohort studies conducted in Europe, reporting on 6 653 207 patients with COVID-19, this systematic review and meta-analyses strengthen the understanding of prognostic factors for adverse outcomes of infection that would set the base for the identification of high-risk populations in order to support public health decision-making regarding booster vaccinations and the application of personal NPIs as societies reopen across Europe.

Extensive research has confirmed the strong association of age and gender with mortality and hospital admissions [104–108], hence it is important to take these factors into account in meta-analyses, particularly given the strong association of COVID-19 outcomes with age, which likely leads to an overestimation of the risk posed by ageing-associated diseases, such as congestive heart disease, COPD and dementia. Hence, in contrast to previous meta-analyses, our approach evaluated the weight of evidence for factors that were at least age-/gender-adjusted to overcome the issue. Notably, male gender was identified as a strong predisposing factor across multiple analyses even after adjusting for patient age.

Hospital and ICU mortality

In our age-/gender-adjusted analyses, increased hospital mortality was noted among patients with COPD, arrhythmia, IHD, heart failure, cancer, renal disease, liver disease, obesity and diabetes. Previous systematic reviews had identified COPD, cardiovascular disease, hypertension, diabetes, chronic renal disease and chronic liver disease as factors associated with mortality in the hospital setting; however, within these reviews, substantial heterogeneity was noted and their results were unadjusted [108–111]. With regards to ICU mortality, our meta-analysis of adjusted data for ICU mortality due to COVID-19 indicated that male gender and the presence of respiratory disease was associated with mortality. However, unadjusted meta-analyses showed associations with several comorbidities, such as COPD and renal disease – results also identified in a recent meta-analysis of unadjusted data on ICU patients which identified hypertension, COPD and cardiovascular disease as prognostic factors of mortality [112]. Whilst obesity has been identified in previous meta-analyses to be strongly associated with mortality [113], within our meta-analyses, the data available for obesity were heterogeneous due to different classifications used within each study. Obesity was associated with overall hospital mortality, supported however only by very low quality of evidence.

Hospital and ICU admission

Our meta-analysis focusing only on European data and evaluating ICU admission indicated that in age-/gender-adjusted analyses, asthma, neurological diseases and autoimmune diseases were associated with an increased likelihood of the need for ICU admission. Furthermore, the need for mechanical ventilation was higher among patients with asthma, liver disease and obesity. These results are different from other ICU cohort data, which may be attributable to our analyses being age-/gender-adjusted [114]; although previous research has also indicated that ICU outcomes may be better predicted by frailty than either age or comorbidity [115]. Notably, our analyses noted that several comorbidities associated with an increased risk of death or hospital admission were not typically associated with an increased incidence of ICU admission or mechanical ventilation. This is not unexpected since patients with pre-existing severe comorbidities may not

be offered ICU admission or mechanical ventilation as therapeutic options during times of unprecedently high pressure on healthcare systems, leading to strict triage criteria [116, 117]. COVID-19, during the first wave of the pandemic, was managed heterogeneously worldwide, especially in resource-constrained countries, where the health systems often had less capacity and fewer resources to face the unfolding pandemic [118]. However, even in the selected high-income countries, ICUs were under unprecedented pressure and strict criteria for selecting patients were applied based on the patients' short-term prognosis [119].

The above results indicate populations of high risk for adverse outcomes and could possibly benefit from potential booster vaccinations as a preventive measure to reduce their elevated risk for adverse COVID-19 outcomes. According to the WHO statement in May 2022, a review of studies on an additional booster dose of mRNA vaccine, which were conducted during the worldwide predominant circulation of Omicron strain, showed benefits in health workers, those over 60 years of age or those with immunocompromising conditions [120]. Moreover, our analyses can further assist to inform planning of patient flows in healthcare settings. Notably, outcomes and prognostic factors in different settings were often different, a factor which may be attributable to several factors. It is possible that the fact that the majority of those contracting SARS-CoV-2 experience a mild or asymptomatic disease, and only a minority progresses to the development of pneumonitis, which may warrant hospital admission [121]. Another potential explanation may be the variability of the impact of different comorbidities on disease progression or clinician bias to the presence of specific comorbidities among patients triaged and on the threshold of hospital admission (*e.g.* a patient with COVID-19 and concomitant COPD is more likely to be admitted than a patient without COPD), indicating a type of selection bias by the clinicians during triage.

Strengths and limitations

Several strengths of our meta-analysis increase our confidence in our findings. The inclusion of only age-/gender-adjusted cohort study data allowed us to control for the primary factor associated with adverse outcomes, which is the patient's age, hence allowing us to assess the independent effect of each prognostic factor [107]. Moreover, we performed separate analyses by clinical setting that allowed us to quantify the incidence of adverse outcomes as separate end-points, which may assist in managing patient flows and triaging. As we applied the GRADE methodology for assessing the evidence about prognostic factors, we rigorously evaluated the certainty of the evidence behind each meta-analysis. Some limitations of our study should also be acknowledged as our results reflect the *status quo* in Europe during the first waves of the pandemic when the Alpha and Beta variants were the most dominant in the largely unvaccinated EU population, hence further research is needed to assess how subsequent vaccination impacts patient mortality. Furthermore, the research identified within this review reflects the Alpha and Beta variants and may not reflect necessarily the risk factors within the post-Omicron strain (B.1.1.529) context. We restricted our inclusion criteria to Europe to enhance the comparability of the results and utility for European clinicians and policymakers, as they have similar healthcare resources, acknowledging that our results may not be generalisable to other areas of the globe. However, similar results have been noted in different geographical areas [108]. Furthermore, there was evidence of heterogeneity as the definition of specific prognostic factors, such as hypertension, obesity and dyslipidaemia, were ambiguous in some of the included studies and variability in the definitions may have also contributed to the observed variability. Given that a direct comparison among different risk factors was not performed and similar effect sizes were found, no conclusions can be drawn on the comparative ranking or cumulative/synergistic effect of specific prognostic factors leading to COVID-19-related adverse outcomes. Nevertheless, conclusions on the individual impact of specific comorbidities can be drawn.

Points for clinical practice

In this systematic review and meta-analysis, only age-/gender-adjusted European cohort study data were used, stratified by clinical setting to control for the primary factor associated with adverse outcomes, which is the patient's age, hence allowing us to assess the independent effect of each prognostic factor. The results of this meta-analysis indicated that COPD, arrhythmia, IHD, heart failure, cancer, renal disease, liver disease, obesity and diabetes were also associated with hospital mortality in age-/gender-adjusted data, while male gender and respiratory diseases were associated with ICU mortality. Additionally, COPD, dyslipidaemia, hypertension, diabetes, cardiovascular disease, obesity, heart failure and male gender were associated with the composite outcome of death and/or ICU admission. This data could be of great significance for European policymakers in terms of prioritisation of preventive public health measures, such as potential booster vaccinations and use of personal NPIs, which could be further refined by accounting for underlining pre-existing conditions in the current as well as future epidemics.

Conclusion

The results of this systematic literature review and meta-analysis of European cohort age-/gender-adjusted data indicate that COPD, arrhythmia, IHD, heart failure, cancer, renal disease, liver disease, obesity and diabetes were associated with hospital mortality while male gender and respiratory diseases were associated with ICU mortality. COPD, dyslipidaemia, hypertension, diabetes, cardiovascular disease, obesity, heart failure and male gender were associated with the composite outcome of death and/or ICU admission. With regards to patient management, factors that were associated with hospital admission included solid organ transplant, sleep apnoea, cardiovascular disease, diabetes, heart failure, respiratory disease and male gender while obesity, asthma and male gender were associated with the need for mechanical ventilation. Taking the above into account, the prioritisation of preventive public health measures, such as potential booster vaccinations and use of personal NPIs, could be further refined by accounting for underlining pre-existing conditions as societies and healthcare systems across Europe continue to face pressure from COVID-19.

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Author contributions: C.I. Vardavas, J. Leonardi-Bee, R. Phalkey and J.E. Suk designed the study. K. Nikitara, D. Carnicer-Pont and A.G. Mathioudakis undertook the literature review and extracted the data. J. Leonardi-Bee and R. Phalkey developed the search code. A.G. Mathioudakis, J. Vestbo, K. Stamatelopoulos and K. Nikitara analysed and interpreted the data. E. Fernandez and G. Georgiopoulos participated in data evaluation and interpretation along with: C.I. Vardavas, J. Leonardi-Bee, R. Phalkey, J.E. Suk, K. Nikitara, K. Stamatelopoulos, and A.G. Mathioudakis. C.I. Vardavas wrote the first draft of the manuscript with input from all authors. J.C. Semenza, C. Deogan, P. Kramarz, F. Lamb and P. Penttinen along with all other authors reviewed and revised subsequent drafts.

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