

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Characteristics and outcomes of COVID-19 patients with and without prevalent hypertension: a multinational cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-057632
Article Type:	Original research
Date Submitted by the Author:	29-Sep-2021
Complete List of Authors:	<p>Reyes, Carlen; GREMPAL Research Group, Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), and CIBERFes, Universitat Autònoma de Barcelona and Instituto de Salud Carlos III,</p> <p>Pistillo, Andrea ; Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol),</p> <p>Fernández-Bertolín, Sergio; Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol),</p> <p>Recalde, Martina</p> <p>Roel, Elena</p> <p>Puente, Diana; IDIAP Jordi Gol, Research</p> <p>Sena, Anthony</p> <p>Blacketer, Clair</p> <p>Lai, Lana</p> <p>Alshammari, Thamir; King Saud University, Medication Safety Research Chair; Saudi Food and Drug Authority,</p> <p>Ahmed, Waheed-UI-Rahman</p> <p>Alser, Osaid ; Harvard Medical School, Trauma, Emergency Surgery and Surgical Critical Care</p> <p>Alghoul, Heba; Islamic University of Gaza Faculty of Medicine,</p> <p>Areia, Carlos; University of Oxford, Nuffield Department of Clinical Neurosciences</p> <p>Dawoud, Dalia; National Institute for Health and Care Excellence,</p> <p>Prats-Urbe, Albert; University of Oxford, Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Science</p> <p>Valveny, Neus</p> <p>de Maeztu, Gabriel</p> <p>Sorlí Redó, Luisa</p> <p>Martinez Roldan, Jordi</p> <p>Lopez Montesinos, Inmaculada</p> <p>Schilling, Lisa</p> <p>Golozar, Asieh; Johns Hopkins University Bloomberg School of Public Health</p> <p>Reich, Christian</p> <p>Posada, Jose</p> <p>Shah, Nigam ; Stanford University,</p> <p>You, Sen Chang</p> <p>Lynch, Kristine; Department of Veterans Affairs; The University of Utah School of Medicine</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

	<p>DuVall, Scott; Department of Veterans Affairs; The University of Utah School of Medicine Matheny, Michael; VA Tennessee Valley Healthcare System, GRECC; Vanderbilt University Medical Center, Department of Biomedical Informatics Nyberg, Fredrik; University of Gothenburg Sahlgrenska Academy, School of Public Health and Community Medicine, Institute of Medicine, Institute of Medicine Ostropolets, Anna Hripcsak, George Rijnbeek, P; Erasmus Medical Center, Rotterdam Suchard, MA; University of California Los Angeles, Ryan, Patrick; Janssen Research and Development LLC, Observational Health Data Analytics; Columbia University Irving Medical Center, Department of Biomedical Informatics Kostka, Kristin Duarte-Salles, Talita; Institut de Recerca en Atencio Primaria Jordi Gol,</p>
Keywords:	COVID-19, EPIDEMIOLOGY, Hypertension < CARDIOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 1 Characteristics and outcomes of COVID-19 patients with and without prevalent
4
5 2 hypertension: a multinational cohort study
6
7 3
8
9

10 4 Carlen Reyes¹, Andrea Pistillo¹, Sergio Fernandez Bertolin¹, Martina Recalde^{1,2}, Elena
11
12 5 Roel^{1,2}, Diana Puente^{1,2}, Anthony G. Sena^{3,4}, Claire Blacketer^{3,4}, Lana YH Lai⁵, Thamer M
13
14 6 Alshammari⁶, Waheed-UI-Rahman Ahmed^{7,8}, Osaid Alser⁹, Heba Alghoul¹⁰, Carlos Areia¹¹,
15
16 7 Dalia Dawoud^{12,13}, Albert Prats-Urbe¹⁴, Neus Valveny¹⁵, Gabriel de Maeztu¹⁶, Luisa Sorlí
17
18 8 Redó^{2,17,18}, Jordi Martínez Roldán¹⁹, Inmaculada Lopez Montesinos¹⁷, Lisa M Schilling²⁰,
19
20 9 Asieh Golozar^{21,22}, Christian Reich²³, Jose D. Posada²⁴, Nigam H. Shah²⁴, Seng Chan You²⁵,
21
22 10 Kristine E. Lynch^{26,27}, Scott L. DuVall^{26,27}, Michael Matheny^{26,27}, Fredrik Nyberg²⁸, Anna
23
24 11 Ostropolets²⁹, George Hripcsak^{30,31}, Peter Rijnbeek³², Mark A. Suchard³³, Patrick Ryan^{3,30},
25
26 12 Kristin Kostka^{23,34}, Talita Duarte-Salles^{1*}
27
28
29
30
31
32

33 14 Affiliations:

- 34
35 15 1- Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i
36
37 Gurina (IDIAPJGol), Barcelona, Spain.
38
39 16
40 17 2- Universitat Autònoma de Barcelona, Spain
41
42
43 18 3- Janssen Research & Development, Titusville, NJ, USA
44
45
46 19 4- Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, The
47
48 Netherlands
49
50 20
51 21 5- School of Medical Sciences, University of Manchester, UK
52
53
54 22 6- College of Pharmacy, Riyadh Elm University Riyadh, Saudi
55
56
57 23 7- Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences,
58
59 University of Oxford, Botnar Research Centre, Windmill Road, Oxford, UK.
60

- 1
- 2
- 3 25 8- College of Medicine and Health, University of Exeter, St Luke's Campus, Heavitree
- 4
- 5 26 Road, Exeter, UK
- 6
- 7
- 8 27 9- Massachusetts General Hospital, Harvard Medical School, USA
- 9
- 10 28 10- Faculty of Medicine, Islamic University of Gaza, Palestine
- 11
- 12 29 11- Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK
- 13
- 14 30 12- National Institute for Health and Care Excellence (NICE), London, UK
- 15
- 16 31 13- Cairo University, Faculty of Pharmacy, Cairo, Egypt
- 17
- 18 32 14- Centre for Statistics in Medicine, NDORMS, University of Oxford, Botnar Research
- 19 33 Centre, Nuffield Orthopaedic Centre, Windmill Road, Oxford, UK
- 20
- 21
- 22 34 15- Real-World Evidence, TFS, Barcelona, Spain
- 23
- 24 35 16- IOMED, Barcelona, Spain
- 25
- 26 36 17- Department of Infectious Diseases, Hospital del Mar, Institut Hospital del Mar
- 27 37 d'Investigació Mèdica (IMIM), Barcelona, Spain
- 28
- 29 38 18- Universitat Pompeu Fabra, Barcelona, Spain
- 30
- 31 39 19- Director of Innovation and Digital Transformation, Hospital del Mar, Barcelona, Spain
- 32
- 33 40 20- University of Colorado Anschutz Medical Campus, Aurora, CO, USA
- 34
- 35 41 21- Regeneron Pharmaceuticals, Tarrytown, NY, USA
- 36
- 37 42 22- Johns Hopkins Bloomberg School of Public health, NY, USA
- 38
- 39 43 23- Real-World Solutions, IQVIA, Cambridge, MA, USA
- 40
- 41 44 24- Stanford University School of Medicine, Stanford, CA, USA
- 42
- 43 45 25- Department of Preventive Medicine, Yonsei University College of Medicine, Seoul,
- 44 46 Korea
- 45
- 46 47 26- VA Informatics and Computing Infrastructure, VA Salt Lake City Health Care System,
- 47 48 Salt Lake City, UT, USA
- 48
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

- 1
2
3 49 27- Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City,
4
5 50 UT, USA
6
7
8 51 28- School of Public Health and Community Medicine, Institute of Medicine, Sahlgrenska
9
10 52 Academy, University of Gothenburg, Gothenburg, Sweden
11
12 53 29- Columbia University Irving Medical Center, New York, USA
13
14 54 30- Department of Biomedical Informatics, Columbia University Irving Medical Center, New
15
16 55 York, NY, USA
17
18 56 31- Medical Informatics Services, NewYork-Presbyterian Hospital, New York, NY, USA
19
20 57 32- Department of Medical Informatics Erasmus University Medical Center, Rotterdam, The
21
22 58 Netherlands
23
24 59 33- Department of Biostatistics, Fielding School of Public Health, University of California,
25
26 60 Los Angeles, USA
27
28 61 34- The OHDSI Center at the Roux Institute, Northeastern University, Portland, ME, USA
29
30
31
32
33
34

35 63 *Corresponding author:

36
37 64 Talita Duarte-Salles

38
39 65 Fundació Institut Universitari per la recerca a L'Atenció Primària de Salut Jordi Gol I Gurina

40
41 66 (IDIAPJGol)

42
43 67 Gran Via Corts Catalanes, 587, àtic

44
45 68 08007 Barcelona-Spain

46
47 69 Tel: +34-93 4824342

48
49 70 Email: tduarte@idiapjgol.org

50
51 71

52
53 72

54
55 73

1
2
3 74 **ABSTRACT**
4

5 75 **Objective:** To characterize patients with and without prevalent hypertension and COVID-19,
6
7
8 76 and to assess their adverse outcomes in both in and outpatients.
9

10 77 **Design and setting:** Retrospective cohort study using 15 healthcare databases (primary and
11
12 78 secondary electronic health care records, insurance and national claims data) from the US,
13
14
15 79 Europe and South Korea, standardized to the Observation Medical Outcomes Partnership
16
17 80 common data model.
18

19
20 81 **Participants:** We included all patients diagnosed/hospitalized with COVID-19 (non-
21
22 82 mutually exclusive cohorts) and stratified them by hypertension status. Follow-up was from
23
24 83 COVID-19 diagnosis/hospitalization to death, end of the study period, or 30-days.
25

26
27 84 **Outcomes:** Demographics, comorbidities, and 30-day outcomes (hospitalization, adverse
28
29 85 events or death) were reported.
30

31
32 86 **Results:** We identified 2,851,035 diagnosed and 563,708 hospitalized patients with COVID-
33
34 87 19. Hypertension was more prevalent in the latter (range (%), 95%CI) across databases 17.4
35
36 88 (17.2-17.6)- 61.4 (61.0-61.8) and 25.6 (24.6-26.6)-85.9 (85.2-86.6). Patients with
37
38 89 hypertension diagnosed with COVID-19 were predominantly >50-year-old and female.
39
40 90 Patients with hypertension were frequently diagnosed with obesity, heart disease,
41
42 91 dyslipidaemia, and diabetes. Compared to patients without hypertension, patients with
43
44 92 hypertension had more hospitalizations (range 1.3 (0.4-2.2)- 41.1 (39.5-42.7) vs 1.4 (0.9-1.9)-
45
46 93 15.9 (14.9-16.9)) and mortality (0.3(0.1-0.5)-18.5 (15.7-21.3) vs 0.2 (0.2-0.2)-11.8 (10.8-
47
48 94 12.8)). Hospitalized patients with hypertension were more likely to have acute respiratory
49
50 95 distress syndrome (0.1(0.0-0.2) -65.6 (62.5-68.7) vs 0.1 (0.0-0.2)-54.7 (50.5-58.9)),
51
52 96 arrhythmia (0.5 (0.3-0.7)-45.8 (42.6-49.0) vs 0.4 (0.3-0.5)-36.8 (32.7-40.9)) and increased
53
54
55
56
57
58
59
60

1
2
3 97 mortality (1.8 (0.4-3.2)-25.1 (23.0-27.2) vs 0.7 (0.5-0.9)-10.9 (10.4-11.4)) than patients
4
5
6 98 without hypertension.

7
8 99 **Conclusions:** COVID-19 patients with hypertension were more likely to suffer severe
9
10
11 100 outcomes, hospitalizations and deaths compared to those without hypertension.

12
13 101 **KEY WORDS:** COVID-19, Epidemiology, Hypertension

14
15
16 102 **WORD COUNT:** 2,971

17
18 103 **ARTICLE SUMMARY**

19
20 104 **Strengths and limitations of this study**

21
22
23 105 1- This study is unique in its approach to characterizing COVID-19 cases across an
24
25 106 international network of healthcare databases, with diverse healthcare systems and
26
27 107 policies, through a comprehensive federated approach.

28
29
30 108 2- This study was carried out using routinely collected clinical practice data, which
31
32 109 confers a great external validity, but also implies a risk of misclassification.

33
34 110 3- This study was intentionally descriptive and was deliberately not designed for causal
35
36 111 inference.

37
38
39 112 4- The diagnosed and/or hospitalized cohorts were non-mutually exclusive.

40
41 113 5- The data that underpinned this study mostly came from the initial months of the
42
43 114 COVID-19 pandemic and may not be representative of the COVID-19 cases
44
45 115 diagnosed and/or hospitalized during subsequent periods.

46
47
48 116 **FUNDING STATEMENT**

49
50 117 This work was supported by several funders as follows; The European Health Data &
51
52 118 Evidence Network received funding from the Innovative Medicines Initiative 2 Joint
53
54
55 119 Undertaking (JU) under grant agreement No 806968. The JU received support from the
56
57 120 European Union's Horizon 2020 research and innovation programme and EFPIA. This
58
59 121 research received partial support from the National Institute for Health Research (NIHR)

1
2
3 122 Oxford Biomedical Research Centre (BRC), US National Institutes of Health (R01
4
5 123 LM006910), US Department of Veterans Affairs, the Health Department from the Generalitat
6
7 124 de Catalunya with a grant for research projects on SARS-CoV-2 and COVID-19 disease
8
9 125 organized by the Direcció General de Recerca i Innovació en Salut, Janssen Research &
10
11 126 Development, TFS, IOMED and IQVIA. The University of Oxford received funding related
12
13 127 to this work from the Bill & Melinda Gates Foundation (Investment ID INV-016201 and
14
15 128 INV-019257). TFS received funding related to this work from the University of Oxford. This
16
17 129 work was also supported with funding, [resources, and facilities] of the Department of
18
19 130 Veterans Affairs (VA) Informatics and Computing Infrastructure (VINCI), VA HSR RES 13-
20
21 131 457. No funders had a direct role in this study. The views and opinions expressed are those of
22
23 132 the authors and do not necessarily reflect those of the Clinician Scientist Award programme,
24
25 133 NIHR, Department of Veterans Affairs or the United States Government, NHS, or the
26
27 134 Department of Health, England.

135 **COMPETING INTERESTS STATEMENT**

136 SLDV reports grants from Anolinx; MS, reports grants from US National Institutes of Health,
137 grants from Department of Veterans Affairs, during the conduct of the study; grants from
138 IQVIA, personal fees from Janssen Research and Development, grants from US Food and
139 Drug Administration, personal fees from Private Health Management, outside the submitted
140 work LLC, grants from Astellas Pharma, Inc, grants from AstraZeneca Pharmaceuticals LP,
141 grants from Boehringer Ingelheim International GmbH, grants from Celgene Corporation,
142 grants from Eli Lilly and Company, grants from Genentech Inc., grants from Genomic
143 Health, Inc., grants from Gilead Sciences Inc., grants from GlaxoSmithKline PLC, grants
144 from Innocrin Pharmaceuticals Inc., grants from Janssen Pharmaceuticals, Inc., grants from
145 Kantar Health, grants from Myriad Genetic Laboratories, Inc., grants from Novartis
146 International AG, grants from Parexel International Corporation through the University of

1
2
3 147 Utah or Western Institute for Veteran Research, outside the submitted work; GH, reports
4
5 148 grants from NIH, during the conduct of the study; grants from Janssen Research, outside the
6
7 149 submitted work; FN, reports that Until 2019 was an employee of AstraZeneca and holds
8
9 150 some AstraZeneca shares, outside the submitted work; KK, reports personal fees from
10
11 151 National Institutes of Health, outside the submitted work, and at the time of data analysis and
12
13 152 initial drafting of the manuscript, KK was an employee of IQVIA Inc; CR reports he is an
14
15 153 employee of IQVIA Inc; GdM is Employee of IOMED; NV is an Employee of TFS; AGS
16
17 154 reports personal fees from Janssen R&D, outside the submitted work and full time employee
18
19 155 of Janssen R&D and is a Johnson and Johnson shareholder; CB reports personal fees from
20
21 156 Janssen R&D, outside the submitted work and is a full time employee of Janssen R&D and is
22
23 157 a Johnson and Johnson shareholder; JDP reports grants from National Library of Medicine,
24
25 158 during the conduct of the study; AG is an employee of Regeneron Pharmaceuticals and
26
27 159 reports stocks from Regeneron Pharmaceuticals. PR reports having received research group
28
29 160 grants from Innovative Medicine Initiative and Janssen Research and Development; MS
30
31 161 reports grants from US National Institutes of Health, grants from Department of Veterans
32
33 162 Affairs, during the conduct of the study; grants from IQVIA, personal fees from Janssen
34
35 163 Research and Development, grants from US Food and Drug Administration, personal fees
36
37 164 from Private Health Management, outside the submitted work; PR, reports and is an
38
39 165 employee of Janssen Research and Development and shareholder of Johnson & Johnson; ER,
40
41 166 SFB, NHS, LMS, DP, SCY, MR, APU, HA, KEL, MM, AO, CA, CR, TDS, TMA, OA, W-
42
43 167 U-RA, ILM, JMR, LSR, DD, LYHL, AP, have nothing to declare. The views expressed are
44
45 168 those of the authors and do not necessarily represent the views or policy of the Department of
46
47 169 Veterans Affairs or the United States Government. No other relationships or activities could
48
49 170 appear to have influenced the submitted work.
50
51
52
53
54
55
56
57
58
59
60

172 INTRODUCTION

173 As of September 2021, the ongoing pandemic of the coronavirus disease 2019 (COVID-19)
174 has affected over 220 million people and the estimated death toll surpasses the 4,5 million
175 deaths worldwide¹. Hypertension is a common chronic condition that may increase the risk of
176 hospitalizations and adverse outcomes². A higher prevalence of hypertension has been found
177 among COVID-19 patients compared to the general population, which has attracted the
178 attention of researchers³. The characterization of this population at risk is key to be able to
179 design effective preventive strategies that could, improve patient outcomes and reduce the
180 pressure on healthcare systems.

181 To date, observational studies⁴⁻¹⁶, systematic reviews, and meta-analyses have reported an
182 increased risk of progression to severe COVID-19 and increased mortality in patients with
183 hypertension¹⁷⁻²¹. However, these studies, either only included hospitalized patients^{4-13,15-16},
184 leading to a selection bias, or had a small sample size^{6-10,15}, both of which limits the
185 extrapolation of results.

186 Most patients with confirmed SARS-CoV-2 infection, experience mild or moderate
187 symptoms (80%)²² and are predominantly seen as outpatients, therefore a large
188 characterization study including both inpatient and outpatients is needed.

189 This study aims to describe and compare the demographics, baseline comorbidities and 30-
190 day outcomes of individuals with COVID-19 and with and without pre-existing hypertension,
191 in both in and outpatients.

192

193 MATERIAL AND METHODS

194 Study design, setting, and data sources

1
2
3 195 A multinational, multi-data base cohort study was conducted using data from 1st March to the
4
5 196 31st October 2020 included in “The Characterizing Health Associated Risks and Your
6
7 197 Baseline Disease In SARS-COV-2” (CHARYBDIS ²³) study. This is a large-scale
8
9
10 198 multinational cohort study aimed to characterize health-associated risks and baseline diseases
11
12 199 in SARS-COV-2 patients using routinely collected primary care and hospital electronic
13
14 200 health records (EHR), hospital billing, and insurance claims data from the United States
15
16 201 (US), Europe (the Netherlands, Spain, the United Kingdom (UK), Germany, and France) and
17
18 202 Asia (South Korea and China).

19
20
21
22 203 From the databases contributing to CHARYBDIS, only twenty had available information on
23
24 204 pre-existing hypertension and were initially selected. To be included in the study, databases
25
26 205 had to: 1. have at least 140 subjects with prevalent hypertension diagnosed with COVID-19
27
28 206 (necessary to estimate the prevalence of previous conditions or 30-day outcomes with
29
30 207 sufficient precision (confidence interval width of $\pm 5\%$) and 2. have at least one year of
31
32
33 208 previous data before the date of COVID-19 diagnosis or hospitalization. Data results for this
34
35 209 paper were extracted on the 21st of January 2021 ²³. Fifteen databases complied with the
36
37 210 aforementioned inclusion criteria. Of these, five had data for outpatients (IQVIA-
38
39 211 Longitudinal Patients Database “LPD” (France), IQVIA-Longitudinal Patients Database
40
41 212 “LPD” (Italy), IQVIA-Disease Analyser “DA” (Germany), Clinical Practice Research
42
43 213 Datalink “CPRD” (UK), Integrated Primary Care Information “IPCI” (the Netherlands), two
44
45 214 had data for in-patients (Health Insurance Review & Assessment Service “HIRA” (South
46
47 215 Korea), Hospital del Mar “HMAR” (Spain)) and eight had both in and out-patient data
48
49 216 (IQVIA-OpenClaims, HEALTHVERITY, Information System for Research in Primary Care
50
51 217 “SIDIAP” (Spain ²⁴), Optum© de-identified Electronic health Record Dataset “OPTUM-
52
53 218 HER” (US), VA-OMOP, University of Colorado Anschutz Medical Campus Health Data
54
55
56
57
58
59
60

1
2
3 219 Compass “CUIMC” (US), CU-AMC-HDC, STANford Medicine Research Data Repository
4
5 220 “STARR-OMOP” (US²⁵). A more detailed description of the included data sources is
6
7
8 221 available in the Supporting Figure 1 and Table 1.

9 10 222 **Study participants and follow-up**

11
12 223 Two non-mutually exclusive cohorts were defined: 1) individuals *diagnosed* with COVID-19
13
14 224 (COVID-19 *diagnosed*) and 2) individuals *hospitalized* with COVID-19 (COVID-19
15
16 225 *hospitalized*). COVID-19 *diagnosed* cohort included individuals with a COVID-19 clinical
17
18 226 diagnosis and/or a SARS-CoV-2 positive test. The COVID-19 *hospitalized* cohort included
19
20 227 patients hospitalized with a COVID-19 clinical diagnosis or positive test 21 days before
21
22 228 admission up to the end of their hospitalization. The codes used to identify COVID-19 cases
23
24 229 are described in more detail in Supporting Table 2. The index date (i.e. cohort start date) was
25
26 230 the date of COVID-19 diagnosis or positive test (whichever occurred first), for the diagnosed
27
28 231 cohort; and the date of hospitalization, for the hospitalized cohort. Cohort participants were
29
30 232 followed from the index date to the earliest of death, the end of the observation period, or 30
31
32 233 days after.

33 34 35 36 37 234 **Baseline characteristics and outcomes of interest**

38
39 235 The hypertension diagnosis, as well as the participants’ sex and age, were gathered at the
40
41 236 index date and identified comorbidities in the year before the index date. Comorbidities
42
43 237 (asthma, cancer, chronic kidney and liver disease, chronic obstructive pulmonary disease,
44
45 238 dementia, heart disease, hyperlipidaemia, peripheral vascular disease, type 2 diabetes
46
47 239 mellitus, obesity) were ascertained based on the Systematized Nomenclature of Medicine
48
49 240 Current Terminology (SNOMED CT) hierarchy, with all descendant codes included. We
50
51 241 selected and included comorbidities based on their prevalence in the cohorts of the
52
53 242 participating sites and their clinical relevance to the COVID-19 research field¹⁷⁻²¹. Clinical
54
55 243 epidemiologists generated a list of codes for the identification of prior medical conditions and
56
57
58
59
60

1
2
3 244 outcomes of interest using a web-based integrated platform (ATLAS tool:
4
5 245 <https://atlas.ohdsi.org/>). The definition of the variables can be found in Supporting Table 3.
6
7
8 246 Our main 30-day outcomes of interest were hospitalization and death for the COVID-19
9
10 247 *diagnosed* cohort, and requirement of intensive services (identified as any record of
11
12 248 mechanical ventilation and/or a tracheostomy and/or extracorporeal membrane oxygenation
13
14 249 procedure), acute respiratory distress syndrome (ARDS), arrhythmia, total cardiovascular
15
16 250 events (ischemic stroke, haemorrhagic stroke, heart failure (heart failure during
17
18 251 hospitalization for the hospitalized cohort), acute myocardial infarction or sudden cardiac
19
20 252 death), sepsis, bleeding, venous thromboembolism (VTE) and death for the COVID-19
21
22 253 *hospitalized* cohort.

26 254 **Statistical analyses**

28 255 All data were standardized to the Observational Medical Outcomes Partnership (OMOP)
29
30 256 Common Data Model (CDM) ²⁶. A common analytical code for the CHARYBDIS study was
31
32 257 developed for the Observational Health Data Sciences and Informatics (OHDSI) Methods
33
34 258 Library which was run locally in each database. Only aggregate results from each database
35
36 259 were publicly shared. The CHARYBDIS protocol and source code can be found at
37
38 260 <https://github.com/ohdsi-studies/Covid19CharacterizationCharybdis>.
39
40
41 261 Demographics (sex and age categorized in 5-year age bands), comorbidities and 30-day
42
43 262 incidence rates of outcomes were reported as proportions, along with 95% Confidence
44
45 263 Intervals (CI). A minimum of 5 individuals was established to minimize the risk of
46
47 264 identification of patients.
48
49
50
51 265 All results are reported by cohort, database and by hypertension status (with or without
52
53 266 hypertension).
54
55
56 267 This is a descriptive study and no causal inference is intended. Multivariable regression or
57
58 268 adjustment for confounding was therefore considered out of remit, and not included in our
59
60

1
2
3 269 study. We used R version 4.0.3 for data visualization. Before performing these analyses, all
4
5 270 the data partners obtained Institutional Review Board (IRB) or equivalent governance
6
7 271 approval. All data partners consented to the external sharing of the result set on
8
9
10 272 data.ohdsi.org. Consent to participate was not required as only anonymised retrospective data
11
12 273 was used for this study and no patient or GP contact was required.

14 274 **Patient and Public Involvement**

16
17 275 No patient involved

19 276 **RESULTS**

21 277 **Study population**

23
24 278 Overall, 2,851,035 patients diagnosed and 563,708 patients hospitalized with COVID-19
25
26 279 were identified in 15 databases from 8 countries (the US, South Korea, Germany, the
27
28 280 Netherlands, France, Italy, Spain, and the UK). In total, 1,408,762 and 427,385 patients
29
30 281 diagnosed and hospitalized with COVID-19, respectively, had a prior diagnosis of
31
32 282 hypertension (Supporting Table 4). The prevalence of hypertension ranged from 17.4% to
33
34 283 48.3% in the COVID-19 *diagnosed* cohort, and from 25.6% to 85.9% in the COVID-19
35
36 284 *hospitalized cohort*.

39 285 **Baseline characteristics**

41
42 286 The age and sex distribution in the COVID-19 *diagnosed cohort* and in the COVID-19
43
44 287 *hospitalized cohort*, with and without hypertension are represented in Figures 1 and 2
45
46 288 respectively. Overall, in both cohorts, patients with hypertension were older than those
47
48 289 without (higher proportion of patients aged above 50 across all databases). The proportion of
49
50 290 patients *diagnosed* with COVID-19 and hypertension peaked at a younger age (55 to 70 years
51
52 291 old) compared to those *hospitalized* (70 to 80 years old). The proportion of women with
53
54 292 hypertension was greater in the *diagnosed* cohort (8.6 % to 55.6%) than in the *hospitalized*
55
56 293 cohort (4.5% to 56%).
57
58
59
60

1
2
3 **294 Baseline comorbidities**

4
5 **295** Figures 3 and 4 reports the proportion of baseline comorbidities of the COVID-19 *diagnosed*
6
7
8 **296** cohort (Figure 3) and COVID-19 *hospitalized* cohort (Figure 4), with and without
9
10 **297** hypertension. Patients with hypertension and COVID-19 *diagnosed* or *hospitalized* were
11
12 **298** frequently diagnosed with obesity, heart disease, dyslipidaemia, and type 2 diabetes, the
13
14 **299** proportion of which, more than double the ones found among patients with COVID-19
15
16
17 **300** without hypertension.

18
19 **301 30-day outcomes of interest**

20
21 **302** Thirty-day outcomes in people with and without hypertension in both the COVID-19
22
23 **303** *diagnosed* and/or *hospitalized* cohorts are reported in Tables 1 and 2.
24
25
26 **304** Patients with hypertension *diagnosed* with COVID-19 were more likely to be hospitalized
27
28 **305** (range 1.3% to 41.1% vs 1.4 to 15.9%) and had increased mortality (range 0.3% to 18.5% vs
29
30 **306** 0.2% to 11.8%) when compared to those without hypertension (Table 1).
31
32

33
34 **Table 1. Comparison of 30-day outcomes of interest between COVID-19 patients with**
35
36 **and without hypertension (HTN), in the COVID-19 diagnosed cohorts in the**
37
38 **CHARYBDIS Network, % (95%CI)**
39

Database	HTN	N	30-day outcomes	
			Death	Hospitalization
IQVIA-OpenClaims (US)	With	1,245,436	-	29.6 (29.5-29.7)
	Without	1,333,227	-	8.9 (8.9-8.9)
OPTUM-HER (US)	With	6,6432	1.7 (1.6-1.8)	26.4 (26.1-26.7)
	Without	11,1033	0.2 (0.2-0.2)	9.2 (9.0-9.4)

VA-OMOP (US)	With	34,093	5.4 (5.2-5.6)	23.4 (23.0-23.8)
	Without	21,464	0.7 (0.6-0.8)	6.1 (5.8-6.4)
HEALTHVERITY (US)	With	25,405	-	14.6 (14.2-15.0)
	Without	88,768	-	3.1 (3.0-3.2)
SIDIAP (Spain)	With	21,289	9.8 (9.4-10.2)	22.8 (22.2-23.4)
	Without	100,852	3.3 (3.2-3.4)	11.2 (11.0-11.4)
CUIMC (US)	With	3,672	11.8 (10.8-12.8)	41.1 (39.5-42.7)
	Without	4,847	2.0 (1.6-2.4)	15.9 (14.9-16.9)
CU-AMC-HDC (US)	With	2,461	5.9 (5.0-6.8)	35.8 (33.9-37.7)
	Without	4,809	0.7 (0.5-0.9)	11.2 (10.3-12.1)
IQVIA-DA (Germany)	With	2,418	0.3 (0.1-0.5)	-
	Without	5,553	-	-
STARR-OMOP (US)	With	1,246	0.6 (0.2-1.0)	24.6 (22.2-27.0)
	Without	2,082	-	14.0 (12.5-15.5)
CPRD (UK)	With	756	18.5 (15.7-21.3)	-
	Without	2,616	11.8 (10.6-13.0)	-
IPCI (The Netherlands)	With	676	13.6 (11.0-16.2)	1.3 (0.4-2.2)
	Without	2,371	3.1 (2.4-3.8)	1.4 (0.9-1.9)

Note: “-” means information is not available or <5 cases for all databases except for CU-AMC HDC where information is not available for <10 cases.

307

308 Patients with hypertension *hospitalized* with COVID-19 were more frequently diagnosed of
309 ARDS (range 0.1 to 65.6% vs 0.1 to 54.7%), cardiac arrhythmia (range 0.5 to 45.8% vs 0.4 to
310 36.8%), and had increased mortality (range 1.8 to 25.1% vs 0.7 to 10.9%) as compared to
311 those without hypertension (Table 2).

Table 2. Comparison of 30-days outcomes of interest between COVID-19 patients with and without hypertension (HTN), in the COVID-19 hospitalized cohorts in the CHARYBDIS Network, % (95%CI)

Database	HTN*	N	30-day outcomes						
			VTE†	Death	Cardiac arrhythmia	Sepsis	ARDS‡	Intensive services	Total CVE§
IQVIA-OpenClaims (US)	With	384,508	3.9 (3.8-4.0)	-	15.4 (15.3-15.5)	18.3 (18.2-18.4)	34.8 (34.6-35.0)	9.1 (9.0-9.2)	11.3 (11.2-11.4)
	Without	118,425	3.8 (3.7-3.9)	-	7.2 (7.1-7.3)	15.5 (15.3-15.7)	31.3 (31.0-31.6)	6.4 (6.3-6.5)	4.5 (4.4-4.6)
OPTUM-HER (US)	With	18,242	6.2 (5.9-6.5)	5.1 (4.8-5.4)	31.6 (30.9-32.3)	24.8 (24.2-25.4)	45.7 (45.0-46.4)	14.0 (13.5-14.5)	18.2 (17.6-18.8)
	Without	10,222	4.4 (4.0-4.8)	1.6 (1.4-1.8)	11.1 (10.5-11.7)	15.0 (14.3-15.7)	27.5 (26.6-28.4)	6.3 (5.8-6.8)	4.8 (4.4-5.2)
VA-OMOP (US)	With	8,996	7.3 (6.8-7.8)	15.4 (14.7-16.1)	33.9 (32.9-34.9)	20.0 (19.2-20.8)	43.9 (42.9-44.9)	17.1 (16.3-17.9)	21.0 (20.2-21.8)
	Without	1,475	6.9 (5.6-8.2)	7.6 (6.2-9.0)	16.8 (14.9-18.7)	16.2 (14.3-18.1)	39.6 (37.1-42.1)	11.2 (9.6-12.8)	7.3 (6.0-8.6)
HEALTHVERITY (US)	With	4,512	3.6 (3.1-4.1)	-	14.8 (13.8-15.8)	16.5 (15.4-17.6)	26.7 (25.4-28.0)	6.1 (5.4-6.8)	11.9 (11.0-12.8)
	Without	3,069	3.9 (3.2-4.6)	-	6.8 (5.9-7.7)	12.5 (11.3-13.7)	23.9 (22.4-25.4)	4.9 (4.1-5.7)	5.6 (4.8-6.4)

SIDIAP (Spain)	With	5,636	1.0 (0.7-1.3)	15.4 (14.5-16.3)	0.5 (0.3-0.7)	-	0.1 (0.0-0.2)	-	0.9 (0.7-1.1)
	Without	12,566	1.1 (0.9-1.3)	10.9 (10.4-11.4)	0.4 (0.3-0.5)	0.0 (0.0-0.0)	0.1 (0.0-0.2)	-	0.5 (0.4-0.6)
CUIMC (US)	With	1,708	3.9 (3.0-4.8)	25.1 (23.0-27.2)	12.1 (10.6-13.6)	6.1 (5.0-7.2)	16.0 (14.3-17.7)	2.2 (1.5-2.9)	8.1 (6.8-9.4)
	Without	892	3.6 (2.4-4.8)	10.2 (8.2-12.2)	4.7 (3.3-6.1)	5.3 (3.8-6.8)	17.8 (15.3-20.3)	1.8 (0.9-2.7)	3.8 (2.5-5.1)
CU-AMC HDC (US)	With	904	11.4 (9.3-13.5)	14.9 (12.6-17.2)	45.8 (42.6-49.0)	34.2 (31.1-37.3)	65.6 (62.5-68.7)	28.3 (25.4-31.2)	19.8 (17.2-22.4)
	Without	530	6.0 (4.0-8.0)	6.0 (4.0-8.0)	36.8 (32.7-40.9)	27.4 (23.6-31.2)	54.7 (50.5-58.9)	15.5 (12.4-18.6)	5.7 (3.7-7.7)
HIRA (South Korea)	With	1,943	0.7 (0.3-1.1)	7.7 (6.5-8.9)	4.4 (3.5-5.3)	5.3 (4.3-6.3)	2.6 (1.9-3.3)	4.9 (3.9-5.9)	10.0 (8.7-11.3)
	Without	5,656	NC	0.7 (0.5-0.9)	0.7 (0.5-0.9)	3.1 (2.6-3.6)	0.5 (0.3-0.7)	0.6 (0.4-0.8)	4.7 (4.1-5.3)
STARR-OMOP (US)	With	342	2.0 (0.5-3.5)	1.8 (0.4-3.2)	22.2 (17.8-26.6)	9.9 (6.7-13.1)	12.6 (9.1-16.1)	9.1 (6.1-12.1)	16.4 (12.5-20.3)
	Without	273	NC	-	6.6 (3.7-9.5)	7.0 (4.0-10.0)	11.4 (7.6-15.2)	5.5 (2.8-8.2)	-
HMAR (Spain)	With	594	3.2 (1.8-4.6)	14.3 (11.5-17.1)	23.1 (19.7-26.5)	1.9 (0.8-3.0)	12.6 (9.9-15.3)	13.5 (10.8-16.2)	12.1 (9.5-14.7)
	Without	1,417	2.6 (1.8-3.4)	3.9 (2.9-4.9)	6.6 (5.3-7.9)	0.7 (0.3-1.1)	7.3 (5.9-8.7)	6.6 (5.3-7.9)	2.2 (1.4-3.0)
Note: “-” means information is not available or <5 cases for all databases except for CU-AMC HDC where information is not available for <10 cases.									

1
2
3 * hypertension; †: Venous thromboembolic (pulmonary embolism and deep vein thrombosis) events; ‡: Acute respiratory distress syndrome; §: cardiovascular disease
4 events
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

For peer review only

1
2
3 **313 DISCUSSION**
4

5 314 This large multinational, multi-database cohort study, reports a greater prevalence of
6
7 315 hypertension among patients *hospitalized* with COVID-19 compared to those *diagnosed* with
8
9 COVID-19. Patients with hypertension diagnosed and/or hospitalized with COVID-19 were
10 316
11 frequently diagnosed with obesity, heart disease, dyslipidaemia, and type 2 diabetes at
12 317
13 baseline, compared to those without hypertension. They were also more likely to experience
14 318
15 adverse outcomes including death and hospitalizations (in the COVID-19 *diagnosed cohort*)
16 319
17 and cardiac arrhythmia, ARDS and death (in the COVID-19 *hospitalized cohort*) than
18 320
19 patients without hypertension.
20 321
21
22

23 322 This is the first large multinational study that characterizes both in and out-patients with
24 323
25 COVID-19, with and without prevalent hypertension. Hypertension was more prevalent in
26 324
27 hospitalized patients compared to those diagnosed with COVID-19 (range from 25.6% to
28 325
29 85.9% vs 17.4 to 61.4% respectively). The observed variability between databases is similar
30 326
31 to previous reports, where prevalence's ranged from 28.8%⁷ to 60%¹⁵.
32 327
33

34 328 However, these results should be put into context given that our highest rate (in both COVID-
35 329
36 19 *diagnosed* and COVID-19 *hospitalized*) was observed in the VA-OMOP database from
37 330
38 the US Department of Veterans Affairs (mostly men of older age).
39 331
40

41 332 As in the general population with hypertension²⁷, patients with hypertension diagnosed with
42 333
43 COVID-19 in this study were more frequently diagnosed with heart disease or type 2 diabetes
44 334
45 at baseline, than individuals without hypertension. These results are similar to what has been
46 335
47 previously published, where patients with hypertension and COVID-19 also reported a higher
48 336
49 prevalence of diabetes mellitus^{6,8,12}, cardiovascular diseases (other than hypertension)^{8,12},
50
51 and chronic kidney disease⁸ compared to those without hypertension. This study further
52
53 expands these previous findings identifying these same comorbidities in the out-patients
54
55
56
57
58
59
60

1
2
3 337 diagnosed with COVID-19 and adds obesity and dyslipidaemia to the list of conditions more
4
5
6 338 frequently found among patients with COVID-19 and hypertension compared to those
7
8 339 without hypertension. The higher prevalence of comorbid conditions found in this study
9
10
11 340 among patients with hypertension *hospitalized* with COVID-19 compared to patients with
12
13 341 hypertension *diagnosed* with COVID-19 suggests a poorer baseline health status.
14
15
16 342 Patients with hypertension *hospitalized* with COVID-19 were more likely to have worse
17
18 343 disease progression with higher rates of ARDS (Prevalence per cent change (PC) between
19
20 344 patients with and without hypertension ranging from -1.8% to 18.2%), more cardiac
21
22 345 arrhythmia (PC ranging from 0.1% to 20.5%) and increased mortality (PC ranging from 3.5%
23
24 346 to 14.9%). Previous studies have documented poorer clinical outcomes in patients with
25
26 347 hypertension hospitalized with COVID-19 (including ARDS)^{8, 12, 14, 19}, the need for
27
28 348 mechanical ventilation, admission to intensive care units^{6, 13, 19} or an increased mortality^{4,7,11-}
29
30 349 ^{13, 19}. This study further showed that patients with hypertension *diagnosed* with COVID-19
31
32 350 were more likely to experience hospitalizations (PC between patients with and without
33
34 351 hypertension ranging from -0.1% to 25.6%), and deaths (PC from 1.5% to 10.5%). These
35
36 352 results highlight the importance of considering hypertension as a possible risk factor in the
37
38 353 overall population *diagnosed* and not only in those *hospitalized* with COVID-19. It also adds
39
40 354 to the current literature cardiac arrhythmia and cardiovascular diseases (other than
41
42 355 hypertension) to the list of adverse outcomes more frequently diagnosed among patients with
43
44 356 hypertension hospitalized with COVID-19 compared to those without hypertension.
45
46 357 This study has several strengths. This is the largest cohort study on individuals with
47
48 358 hypertension who were *diagnosed* and/or *hospitalized* with COVID-19 to date. It provides
49
50 359 novel insight into the characterization of patients *diagnosed* with COVID-19 and confers a
51
52 360 greater external validity of its results compared to what has been published up to date (only
53
54 361 *hospitalized* patients). It is also unique in its approach to characterizing COVID-19 cases
55
56
57
58
59
60

1
2
3 362 across an international network of healthcare databases, with diverse healthcare systems and
4
5 363 policies, through a comprehensive federated approach, allowing the analysis of 15 databases
6
7 364 without sharing patient identifiable data, hence respecting the patients' confidentiality at all
8
9 365 times.

10
11
12 366 We recognize there are limitations to our approach. First, this study was intentionally
13
14 367 descriptive and was deliberately not designed for causal inference. The observed differences
15
16 368 between groups (eg. with versus without hypertension) should therefore not be interpreted as
17
18 369 causal effects. Our patients were analysed depending on if they were *diagnosed* and/or
19
20 370 *hospitalized* with COVID-19 according to database registration procedures, however,
21
22 371 variations could have occurred during the processes by which patients were screened, tested,
23
24 372 admitted, and registered across time and the databases. Additionally, the diagnosed and/or
25
26 373 hospitalized cohorts were non-mutually exclusive, and therefore could be patients in the
27
28 374 diagnosed cohort who were also hospitalized and vice versa.

29
30
31 375 This study was carried out using data recorded in routine clinical practice based on EHRs
32
33 376 and/or claims, therefore, data could be incomplete or be erroneous, leading to potential
34
35 377 misclassification. We have therefore selectively reported database-specific outcomes to
36
37 378 minimize the impact of incompleteness. Differential reporting in databases is likely due to
38
39 379 different coding practices as well as variability in disease severity, with milder/less
40
41 380 symptomatic cases more likely being only diagnosed, and more severe ones hospitalized.
42
43 381 Finally, the data that underpinned this study mostly came from the initial months of the
44
45 382 COVID-19 pandemic and may not be representative of the COVID-19 cases diagnosed
46
47 383 and/or hospitalized during subsequent periods.

384 **CONCLUSIONS**

385 COVID-19 patients with hypertension are more likely to have comorbidities, experience
386 more severe outcomes including hospitalizations and deaths (among outpatients with

1
2
3 387 COVID-19) and experience more ARDS and deaths (among inpatients' with COVID-19)
4
5 388 compared with patients without hypertension.
6
7
8 389

9
10 390 **FIGURE LEGENDS**

11
12 391 **Figure 1. Comparison of the age and sex distribution in patients with a COVID-19**
13
14 392 **diagnosis with and without hypertension in the CHARYBDIS Network, %.** Colour Red=
15
16 393 with hypertension, Green= without hypertension.

17
18 394 **Figure 2. Comparison of the age and sex distribution in patients with a COVID-19**
19
20 395 **hospitalization with and without hypertension in the CHARYBDIS Network, %.** Colour
21
22 396 Red=with hypertension, Colour Green=without hypertension.

23
24 397 **Figure 3. Comorbidities at baseline among patients with a COVID-19 diagnosis with**
25
26 398 **and without hypertension in the CHARYBDIS Network, %.** Colour Red=with
27
28 399 hypertension, Colour Green=without hypertension.

29
30 400 **Figure 4. Comorbidities at baseline among patients with a COVID-19 hospitalization**
31
32 401 **with and without hypertension in the CHARYBDIS Network, %.** Colour Red=with
33
34 402 hypertension, Colour Green=without hypertension.
35
36
37
38
39

40 403
41
42 404 **CONTRIBUTOR'S STATEMENT**

43
44 405 CR, AGS, CA, APU, AG, FN, AO, GH, PR, KK, TDS, KEL, SLD, MR, ER, SFB and AP
45
46 406 provided substantial contributions to the conception or design, analysis, and interpretation of
47
48 407 data for the work. CR, AGS, CA, APU, AG, FN, AO, GH, PR, KK, TDS, KEL, SLD, MR,
49
50 408 ER, SFB, AP, DP, NV, GdeM, LSR, JPH, JMR, ILM, NHS, PRy, MAS, MM, CB, LYHL,
51
52 409 TLA, W-U-RA, OA, HA, DD drafted or revised the manuscript critically for important
53
54 410 intellectual content. All authors approved the final version of the manuscript and CR, AGS,
55
56 411 CA, APU, AG, FN, AO, GH, PR, KK, TDS, LYHL, TLA, W-U-RA, OA, HA, DD, LMS,
57
58
59
60

1
2
3 412 CRei, JDP, SCY agreed to be accountable for all aspects of the work (KEL and SLD only for
4
5 413 VA data) in ensuring that questions related to the accuracy or integrity of any part of the
6
7
8 414 work are appropriately investigated and resolved.
9

10 415

11 416 **ACKNOWLEDGEMENTS**

12
13
14 417 We would like to acknowledge the patients who suffered from or died of this devastating
15
16 418 disease, and their families and carers. We also thank the healthcare professionals involved in
17
18 419 the management of COVID-19 during these challenging times, from primary care to intensive
19
20 420 care units. The authors appreciate the Korean Health Insurance Review and Assessment
21
22 421 Service for providing data.
23

24
25 422 We also thank the database curation teams around the world including the COVIDMAR
26
27 423 Group (JPHorcajada, R.Güerri, J.Villar, M.Montero, S.Gómez-Zorrilla, M.Arenas-Miras,
28
29 424 J.Gómez-Junyent, I.Arrieta, E.Sendra, S.Castañeda, E.Letang, I.Pelegrín, A.Rial,
30
31 425 J.Rodríguez, C.Gimenez, J.Soldado, E.García).
32

33 426 We also thank the important contribution to this work of Dr Daniel Prieto-Alhambra.
34
35
36
37
38 427

39 428 **DATA SHARING STATEMENT**

40
41
42 429 Open Science is a guiding principle within OHDSI. As such, we provide unfettered access to
43
44 430 all open-source analysis tools employed in this study via

45
46 431 <https://github.com/ohdsi-studies/Covid19CharacterizationCharybdis>, as well as all data and

47
48 432 results artefacts that do not include patient-level health information via

49
50 433 <https://data.odhsi.org/Covid19CharacterizationCharybdis/>. Data partners contributing to this

51
52 434 study remain custodians of their individual patient-level health information and hold either

53
54 435 IRB exemption or approval for participation.
55
56
57
58 436

1
2
3 **437 REFERENCES**

- 4
5 **438** 1- Weekly Operational Update on COVID-19-6 Sep 2021 [internet]. WHO [cited 9th
6
7
8 **439** September 2021]. Available from [https://www.who.int/publications/m/item/weekly-](https://www.who.int/publications/m/item/weekly-operational-update-on-covid-19---6-september-2021)
9
10 **440** [operational-update-on-covid-19---6-september-2021](https://www.who.int/publications/m/item/weekly-operational-update-on-covid-19---6-september-2021).
11
12
13 **441** 2- Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020
14
15 **442** International Society of Hypertension global hypertension practice guidelines. *J Hypertens.*
16
17 **443** 2020;38:982-1004.
18
19
20 **444** 3-Cook TM. The importance of hypertension as a risk factor for severe illness and mortality
21
22 **445** in COVID-19. *Anaesthesia.* 2020;75:976-977.
23
24
25 **446** 4-Gupta S, Hayek SS, Wang W, Chan L, Mathews KS, Melamed ML, et al. Factors
26
27 **447** Associated With Death in Critically Ill Patients With Coronavirus Disease 2019 in the US.
28
29 **448** *JAMA Intern Med.* 2020;180:1–12.
30
31
32 **449** 5-Jiménez E, Fontán-Vela M, Valencia J, Fernandez-Jimenez I, Álvaro-Alonso EA,
33
34 **450** Izquierdo-García E, et al. Characteristics, complications and outcomes among 1549 patients
35
36 **451** hospitalised with COVID-19 in a secondary hospital in Madrid, Spain: a retrospective case
37
38 **452** series study. *BMJ Open.* 2020;10:e042398.
39
40
41 **453** 6-Huang S, Wang J, Liu F, Liu J, Cao G, Yang C, et al. COVID-19 patients with
42
43 **454** hypertension have more severe disease: a multicenter retrospective observational study.
44
45 **455** *Hypertens Res.* 2020;43:824-831.
46
47
48 **456** 7-Park BE, Lee JH, Park HK, Kim HN, Jang SY, Bae MH, et al. Impact of Cardiovascular
49
50 **457** Risk Factors and Cardiovascular Diseases on Outcomes in Patients Hospitalized with
51
52 **458** COVID-19 in Daegu Metropolitan City. *J Korean Med Sci.* 2021;36:e15.
53
54
55
56
57
58
59
60

- 1
2
3 459 8- Yao Q, Ni J, Hu TT, Cai ZL, Zhao JH, Xie QW, et al. Clinical characteristics and
4
5
6 460 outcomes in coronavirus disease 2019 (COVID-19) patients with and without hypertension: a
7
8 461 retrospective study. *Rev Cardiovasc Med.* 2020;21:615-625.
9
10
11 462 9- Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for
12
13 463 mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.
14
15 464 *Lancet.* 2020;395(10229):1054-1062.
16
17
18 465 10-Wang Y, Lu X, Li Y, Chen H, Chen T, Su N, et al. Clinical Course and Outcomes of 344
19
20 466 Intensive Care Patients with COVID-19. *Am J Respir Crit Care Med.* 2020;201:1430-1434.
21
22
23 467 11-Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline
24
25 468 Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to
26
27 469 ICUs of the Lombardy Region, Italy. *JAMA.* 2020;323:1574-1581.
28
29
30 470 12-Gao C, Cai Y, Zhang K, Zhou L, Zhang Y, Zhang X, et al. Association of hypertension
31
32 471 and antihypertensive treatment with COVID-19 mortality: a retrospective observational
33
34 472 study. *Eur Heart J.* 2020;41:2058-2066.
35
36
37 473 13- Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its
38
39 474 impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J.*
40
41 475 2020;55:2000547.
42
43
44 476 14- Ji W, Huh K, Kang M, Hong J, Bae GH, Lee R, et al. Effect of Underlying Comorbidities
45
46 477 on the Infection and Severity of COVID-19 in Korea: a Nationwide Case-Control Study. *J*
47
48 478 *Korean Med Sci.* 2020;35:e237.
49
50
51 479 15- Chilimuri S, Sun H, Alemam A, Mantri N, Shehi E, Tejada J, et al. Predictors of
52
53 480 Mortality in Adults Admitted with COVID-19: Retrospective Cohort Study from New York
54
55 481 City. *West J Emerg Med.* 2020;21:779-784.
56
57
58
59
60

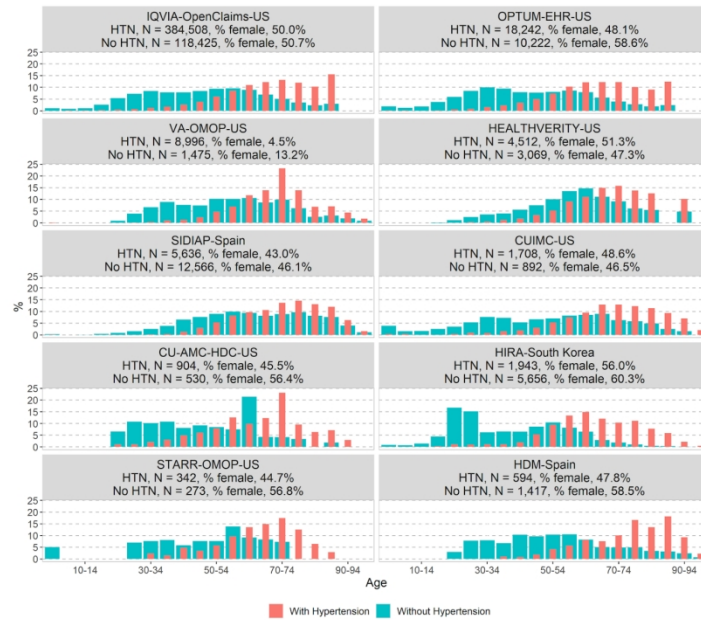
- 1
2
3 482 16- Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al.
4
5
6 483 Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized
7
8 484 With COVID-19 in the New York City Area. *JAMA*. 2020;323:2052-2059. Erratum in:
9
10 485 *JAMA*. 2020;323:2098.
11
12
13 486 17-Dorjee K, Kim H, Bonomo E, Dolma R. Prevalence and predictors of death and severe
14
15 487 disease in patients hospitalized due to COVID-19: A comprehensive systematic review and
16
17 488 meta-analysis of 77 studies and 38,000 patients. *PLoS One*. 2020;15:e0243191.
18
19
20 489 18-Javanmardi F, Keshavarzi A, Akbari A, Emami A, Pirbonyeh N. Prevalence of underlying
21
22 490 diseases in dead cases of COVID-19: A systematic review and meta-analysis. *PLoS One*.
23
24 491 2020;15:e0241265.
25
26
27 492 19-Pranata R, Lim MA, Huang I, Raharjo SB, Lukito AA. Hypertension is associated with
28
29 493 increased mortality and severity of disease in COVID-19 pneumonia: A systematic review,
30
31 494 meta-analysis and meta-regression. *J Renin Angiotensin Aldosterone Syst*.
32
33 495 2020;21:1470320320926899.
34
35
36 496 20- Silverio A, Di Maio M, Citro R, Esposito L, Iuliano G, Bellino M, et al. Cardiovascular
37
38 497 risk factors and mortality in hospitalized patients with COVID-19: systematic review and
39
40 498 meta-analysis of 45 studies and 18,300 patients. *BMC Cardiovasc Disord*. 2021;21:23.
41
42
43 499 21- Moazzami B, Chaichian S, Kasaeian A, Djalalinia S, Akhlaghdoust M, Eslami M, et al.
44
45 500 Metabolic risk factors and risk of Covid-19: A systematic review and meta-analysis. *PLoS*
46
47 501 *One*. 2020;15:e0243600.
48
49
50 502 22- Baj J, Karakuła-Juchnowicz H, Teresiński G, Buszewicz G, Ciesielka M, Sitarz E, et al.
51
52 503 COVID-19: Specific and Non-Specific Clinical Manifestations and Symptoms: The Current
53
54 504 State of Knowledge. *J Clin Med*. 2020;9:1753.
55
56
57
58
59
60

- 1
2
3 505 23- Prieto-Alhambra D, Kostka K, Duarte-Salles T, Prats-Urbe A, Sena A, Pistillo A, et al.
4
5 506 Unraveling COVID-19: a large-scale characterization of 4.5 million COVID-19 cases using
6
7 507 CHARYBDIS. Res Sq [Preprint]. 2021:rs.3.rs-279400.
8
9
10 508 24- García-Gil M del M, Hermosilla E, Prieto-Alhambra D, Fina F, Rosell M, Ramos R, et al.
11
12 509 Construction and validation of a scoring system for the selection of high-quality data in a
13
14 510 Spanish population primary care database (SIDIAP). Inform Prim Care. 2011; 19(3): 135–45
15
16
17 511 25-Datta S, Posada J, Olson G, Li W, O'Reilly C, Balraj D, et al. A new paradigm for
18
19 512 accelerating clinical data science at Stanford Medicine. arXiv:2003.10534
20
21
22 513 26-Voss EA, Makadia R, Matcho A, Ma Q, Knoll C, Schuemie M, et al. Feasibility and
23
24 514 utility of applications of the common data model to multiple, disparate observational health
25
26 515 databases. J Am Med Inform Assoc. 2015;22:553-64.
27
28
29 516 27-Tsimihodimos V, Gonzalez-Villalpando C, Meigs JB, Ferrannini E. Hypertension and
30
31 517 Diabetes Mellitus: Coprediction and Time Trajectories. Hypertension. 2018;71:422-428.
32
33 518
34
35 519
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



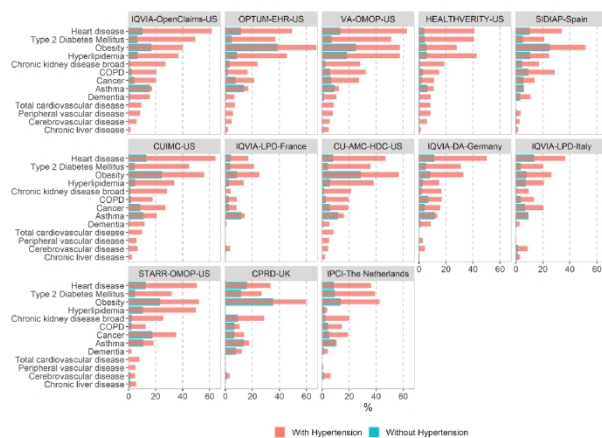
Comparison of the age and sex distribution in patients with a COVID-19 diagnosis with and without hypertension in the CHARYBDIS Network, %. Colour Red= with hypertension, Green= without hypertension.

531x752mm (79 x 79 DPI)



Comparison of the age and sex distribution in patients with a COVID-19 hospitalization with and without hypertension in the CHARYBDIS Network, %. Colour Red=with hypertension, Colour Green=without hypertension.

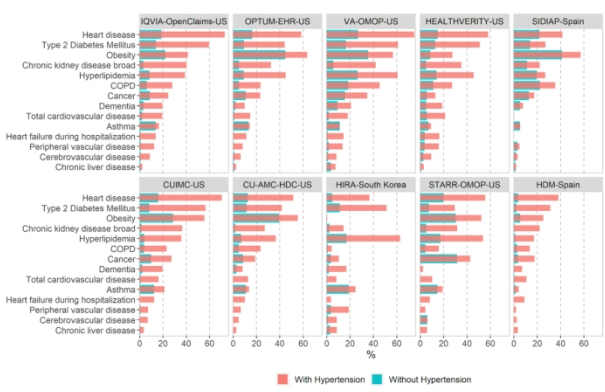
532x752mm (79 x 79 DPI)



Comorbidities at baseline among patients with a COVID-19 diagnosis with and without hypertension in the CHARYBDIS Network, %. Colour Red=with hypertension, Colour Green=without hypertension.

210x297mm (300 x 300 DPI)

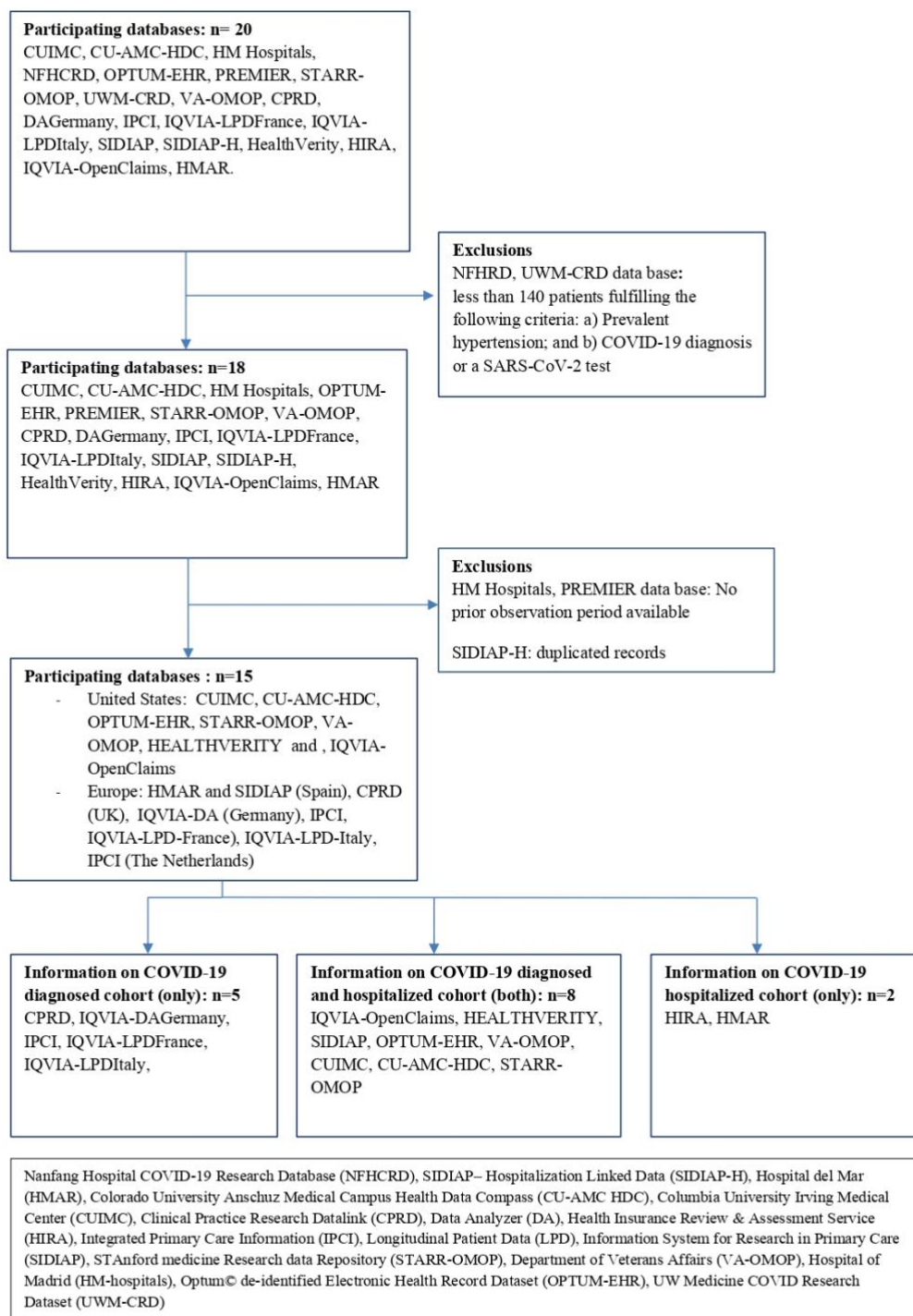
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



Comorbidities at baseline among patients with a COVID-19 hospitalization with and without hypertension in the CHARYBDIS Network, %. Colour Red=with hypertension, Colour Green=without hypertension.

532x752mm (79 x 79 DPI)

Supporting Figure 1. Flowchart showing the selection of databases included in the analyses



Supporting Table 1. Description of included databases

Institution Name/ Database	Database Description	Country
Janssen Research & Development The Clinical Practice Research Datalink (CPRD)	The Clinical Practice Research Datalink (CPRD) is a governmental not-for-profit research service jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA) a part of the Department of Health United Kingdom (UK). CPRD consists of data collected from UK primary care for all ages. This includes conditions observations measurements and procedures that the general practitioner is made aware of in addition to any prescriptions as prescribed by the general practitioner. In addition to primary care there are also linked secondary care records for a small number of people. The major data elements contained within this database are outpatient prescriptions given by the general practitioner (coded with Multilex codes) and outpatient clinical referral immunization or test events that the general practitioner knows about (coded in Read or ICD10 or LOINC codes). The database also contains the patients' year of births and any date of deaths.	United Kingdom
IDIAPJGol The Information System for Research in Primary Care (SIDIAP)	The Information System for Research in Primary Care (SIDIAP; www.sidiap.org) is a primary care records database that covers approximately 80% of the population of Catalonia North-East Spain. Healthcare is universal and tax-payer funded in the region and primary care physicians are gatekeepers for all care and responsible for repeat prescriptions.	Spain
Stanford Medicine Research Data Repository (STARR-OMOP)	A clinical data warehouse containing live Epic data from Stanford Health Care the Stanford Children's Hospital	United States

	the University Healthcare Alliance and Packard Children's Health Alliance clinics. Reference: Datta S Posada J Olson G <i>et al.</i> A new paradigm for accelerating clinical data science at Stanford Medicine. <i>arXiv</i> 2020; published online March 17. http://arxiv.org/abs/2003.10534 (accessed Aug 20 2020).	
Columbia University Irving Medical Center (CUIMC)	The clinical data warehouse of New York-Presbyterian Hospital/Columbia University Irving Medical Center New York NY based on its current and previous electronic health record systems with data spanning over 30 years and including over 6 million patients	United States
IQVIA Open Claims	Pre-adjudicated claims covering over 300 Million lives (~80% of the US) collected from office-based physicians and specialists via office management software and clearinghouse switch sources for the purpose of reimbursement.	United States
HIRA Health Insurance Review & Assessment Service	National claim data from a single insurance service from South Korea, It contains the observational medical records (including both inpatient and outpatient) of a patient while they are qualified to get the national medical insurance.	South Korea
HMAR Hospital del mar	Anonymized data from the Electronic Medical Records from Hospital del Mar (Barcelona, Spain). Hospital belonging to the Spanish National Health System (public), attending the Eastern area of Barcelona City. Includes hospital data collected routinely in the clinical practice, both structured and unstructured information, extracted using a free text analysis tool (with natural language processing): Inpatient (hospital) care, Outpatient specialist care, Emergency Room Visits and partial information from other settings like primary care and pharmacy care present in free text notes from EMRs. All subjects with at least one healthcare encounter with the Hospital within approximately last 20 years are included (approximately 0.6 M subjects, with more than	Spain

	5 M hospitalizations/visits). Hospital del Mar data are made available through collaboration with TFS / IOMED.	
OPTUM-EHR Optum® de-identified Electronic Health Record Dataset	Optum ® de-identified Electronic Health Record Dataset is derived from dozens of healthcare provider organizations in the United States (that include more than 700 hospitals and 7,000 Clinics treating more than 103 million patients) receiving care in the United States. The medical record data includes clinical information, inclusive of prescriptions as prescribed and administered, lab results, vital signs, body measurements, diagnoses, procedures, and information derived from clinical Notes using Natural Language Processing (NLP)	United States
IPCI Integrated Primary Care Information	The Integrated Primary Care Information (IPCI) database is collected from EHR records of patients registered with 391 GPs throughout the Netherlands. The database contains records from approximately 2.6 million patients out of a Dutch population of 17M (8.2%) starting in 1996.	The Netherlands
DA Germany IQVIA Disease Analyser Germany	IQVIA DA Germany is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings. Data coverage includes more than 34M distinct person records out of a total population of 80M (42.5%) in the country and collected from 2,734 providers. Dates of service include from 1992 through March 2020	Germany
LPD-Italy IQVIA LPD Italy	LPD Italy is comprised of anonymised patient records collected from software used by GPs during an office visit to document patients' clinical records. Data coverage includes over 2M patient records with at least one visit and 119.5M prescription orders across 900 GP practices. Dates of service include from 2004 through	Italy

	present. Observation time is defined by the first and last consultation dates. Drugs are captured as prescription records with product, quantity, dosing directions, strength, indication and date of consultation.	
LPD-France	LPD France is a computerised network of physicians including GPs who contribute to a centralised database of anonymised patient EMR. Currently, >1200 GPs from 400 practices are contributing to the database covering 7.8M patients in France. The database covers a time period from 1994 through the present. Observation time is defined by the first and last consultation dates. Drug information is derived from GP prescriptions. Drugs obtained over the counter by the patient outside the prescription system are not reported	France
HEALTHVERITY	This HealthVerity derived data set contains de-identified patient information with an antibody and/or diagnostic test for COVID-19 linked to all available Medical Claims and Pharmacy Data from select private data providers participating in the HealthVerity marketplace.	United States
University of Colorado Anschutz Medical Campus Health Data Compass (CU-AMC HDC)	Health Data Compass (HDC) is a multi-institutional data warehouse. HDC contains inpatient and outpatient electronic medical data including patient, encounter, diagnosis, procedures, medications, laboratory results from two electronic medical record systems (UCHealth and Children's Hospital of Colorado), state-level all-payers claims data, and the Colorado death registry. Acknowledgement statement: Supported by the Health Data Compass Data Warehouse project (healthdatacompass.org)	
Department of Veterans Affairs VA- OMOP	VA-OMOP data reflects the national Department of Veterans Affairs health care system which is the largest integrated provider of medical and mental health services	United States

in the United States. Care is provided at 170 VA Medical Centers and 1 063 outpatient sites serving more than 9 million enrolled Veterans each year.

Supporting Table 2. Definitions and codes used to identify COVID-19 cases

The below tables summarises the concepts used to identify patients diagnosed with COVID-19 . The full description of the logic used to identify patients diagnosed and hospitalized is provided at <https://atlas.ohdsi.org/#/cohortdefinition/200> and <https://atlas.ohdsi.org/#/cohortdefinition/197> respectively.

COVID-19 condition codes		
Id	Name	Vocabulary
756023	Acute bronchitis due to COVID-19	OMOP Extension
756044	Acute respiratory distress syndrome (ARDS) due to COVID-19	OMOP Extension
756061	Asymptomatic COVID-19	OMOP Extension
756031	Bronchitis due to COVID-19	OMOP Extension
439676	Coronavirus infection	SNOMED
37311061	Disease caused by 2019-nCoV	SNOMED
4100065	Disease due to Coronaviridae	SNOMED
37310284	Encephalopathy caused by 2019 novel coronavirus	SNOMED

37310283	Gastroenteritis caused by 2019 novel coronavirus	SNOMED
4248811	Healthcare associated severe acute respiratory syndrome	SNOMED
756081	Infection of lower respiratory tract due to COVID-19	OMOP Extension
37310286	Infection of upper respiratory tract caused by 2019 novel coronavirus	SNOMED
45763594	Middle East respiratory syndrome	SNOMED
37310287	Myocarditis caused by 2019 novel coronavirus	SNOMED
37310254	Otitis media caused by 2019 novel coronavirus	SNOMED
37310285	Pneumonia caused by 2019 novel coronavirus	SNOMED
37016927	Pneumonia caused by Human coronavirus	SNOMED
40479642	Pneumonia due to Severe acute respiratory syndrome coronavirus	SNOMED
756039	Respiratory infection due to COVID-19	OMOP Extension
320651	Severe acute respiratory syndrome	SNOMED
37396171	Severe acute respiratory syndrome of upper respiratory tract	SNOMED
37311060	Suspected disease caused by 2019-nCoV	SNOMED
COVID-19 specific testing - Positive		
37310282	2019 novel coronavirus detected	SNOMED
COVID-19 specific testing (note these required a corresponding value as concept of: Detected Positive or Present)		

37310255	Detection of 2019 novel coronavirus using polymerase chain reaction technique	SNOMED
700360	Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) amplified probe technique	CPT4
37310258	Measurement of 2019 novel coronavirus antibody	SNOMED
37310257	Measurement of 2019 novel coronavirus antigen	SNOMED
756055	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	OMOP Extension
586310	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Genetic material using Molecular method	OMOP Extension
704991	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Blood	OMOP Extension
756029	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Respiratory specimen	OMOP Extension
586307	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Saliva	OMOP Extension
705107	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Sample from nose	OMOP Extension
586309	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Specified specimen	OMOP Extension
756065	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Unspecified specimen	OMOP Extension
704992	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Culture method	OMOP Extension
705001	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique	OMOP Extension
705000	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Blood	OMOP Extension
756085	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Respiratory specimen	OMOP Extension
586308	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Saliva	OMOP Extension
705106	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Sample from nose	OMOP Extension
756084	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Unspecified specimen	OMOP Extension
704993	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Sequencing	OMOP Extension

586516	SARS-CoV-2 (COVID19) [Presence] in Unspecified specimen by Organism specific culture	LOINC
723480	SARS-CoV-2 (COVID19) Ab [Interpretation] in Serum or Plasma	LOINC
586515	SARS-CoV-2 (COVID19) Ab [Presence] in Serum or Plasma by Immunoassay	LOINC
586522	SARS-CoV-2 (COVID19) Ab [Units/volume] in Serum or Plasma by Immunoassay	LOINC
706179	SARS-CoV-2 (COVID19) Ab panel - Serum or Plasma by Immunoassay	LOINC
723477	SARS-CoV-2 (COVID19) Ag [Presence] in Respiratory specimen by Rapid immunoassay	LOINC
706166	SARS-CoV-2 (COVID19) E gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	LOINC
586523	SARS-CoV-2 (COVID19) E gene [Presence] in Respiratory specimen by NAA with probe detection	LOINC
586518	SARS-CoV-2 (COVID19) E gene [Presence] in Serum or Plasma by NAA with probe detection	LOINC
706174	SARS-CoV-2 (COVID19) E gene [Presence] in Unspecified specimen by NAA with probe detection	LOINC
723473	SARS-CoV-2 (COVID19) IgA Ab [Presence] in Serum or Plasma by Immunoassay	LOINC
586521	SARS-CoV-2 (COVID19) IgA Ab [Presence] in Serum Plasma or Blood by Rapid immunoassay	LOINC
723459	SARS-CoV-2 (COVID19) IgA Ab [Units/volume] in Serum or Plasma by Immunoassay	LOINC
757686	SARS-CoV-2 (COVID19) IgA+IgM [Presence] in Serum or Plasma by Immunoassay	LOINC
586527	SARS-CoV-2 (COVID19) IgG Ab [Presence] in DBS by Immunoassay	LOINC
723474	SARS-CoV-2 (COVID19) IgG Ab [Presence] in Serum or Plasma by Immunoassay	LOINC
706181	SARS-CoV-2 (COVID19) IgG Ab [Presence] in Serum Plasma or Blood by Rapid immunoassay	LOINC
706177	SARS-CoV-2 (COVID19) IgG Ab [Units/volume] in Serum or Plasma by Immunoassay	LOINC
706176	SARS-CoV-2 (COVID19) IgG and IgM panel - Serum Plasma or Blood by Rapid immunoassay	LOINC
723479	SARS-CoV-2 (COVID19) IgG+IgM Ab [Presence] in Serum or Plasma by Immunoassay	LOINC

723475	SARS-CoV-2 (COVID19) IgM Ab [Presence] in Serum or Plasma by Immunoassay	LOINC
706180	SARS-CoV-2 (COVID19) IgM Ab [Presence] in Serum Plasma or Blood by Rapid immunoassay	LOINC
706178	SARS-CoV-2 (COVID19) IgM Ab [Units/volume] in Serum or Plasma by Immunoassay	LOINC
706167	SARS-CoV-2 (COVID19) N gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	LOINC
706157	SARS-CoV-2 (COVID19) N gene [Cycle Threshold #] in Unspecified specimen by Nucleic acid amplification using CDC primer-probe set N1	LOINC
706155	SARS-CoV-2 (COVID19) N gene [Cycle Threshold #] in Unspecified specimen by Nucleic acid amplification using CDC primer-probe set N2	LOINC
715272	SARS-CoV-2 (COVID19) N gene [Presence] in Nasopharynx by NAA with probe detection	LOINC
757678	SARS-CoV-2 (COVID19) N gene [Presence] in Nose by NAA with probe detection	LOINC
706161	SARS-CoV-2 (COVID19) N gene [Presence] in Respiratory specimen by NAA with probe detection	LOINC
586524	SARS-CoV-2 (COVID19) N gene [Presence] in Respiratory specimen by Nucleic acid amplification using CDC primer-probe set N1	LOINC
586525	SARS-CoV-2 (COVID19) N gene [Presence] in Respiratory specimen by Nucleic acid amplification using CDC primer-probe set N2	LOINC
586520	SARS-CoV-2 (COVID19) N gene [Presence] in Serum or Plasma by NAA with probe detection	LOINC
706175	SARS-CoV-2 (COVID19) N gene [Presence] in Unspecified specimen by NAA with probe detection	LOINC
706156	SARS-CoV-2 (COVID19) N gene [Presence] in Unspecified specimen by Nucleic acid amplification using CDC primer-probe set N1	LOINC
706154	SARS-CoV-2 (COVID19) N gene [Presence] in Unspecified specimen by Nucleic acid amplification using CDC primer-probe set N2	LOINC
757680	SARS-CoV-2 (COVID19) neutralizing antibody [Presence] in Serum by pVNT	LOINC
757679	SARS-CoV-2 (COVID19) neutralizing antibody [Titer] in Serum by pVNT	LOINC
723469	SARS-CoV-2 (COVID19) ORF1ab region [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	LOINC
706168	SARS-CoV-2 (COVID19) ORF1ab region [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	LOINC
723478	SARS-CoV-2 (COVID19) ORF1ab region [Presence] in Respiratory specimen by NAA with probe detection	LOINC

723464	SARS-CoV-2 (COVID19) ORF1ab region [Presence] in Unspecified specimen by NAA with probe detection	LOINC
723471	SARS-CoV-2 (COVID19) RdRp gene [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	LOINC
723470	SARS-CoV-2 (COVID19) RdRp gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	LOINC
706160	SARS-CoV-2 (COVID19) RdRp gene [Presence] in Respiratory specimen by NAA with probe detection	LOINC
706173	SARS-CoV-2 (COVID19) RdRp gene [Presence] in Unspecified specimen by NAA with probe detection	LOINC
586528	SARS-CoV-2 (COVID19) RNA [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	LOINC
586529	SARS-CoV-2 (COVID19) RNA [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	LOINC
715262	SARS-CoV-2 (COVID19) RNA [Log #/volume] (viral load) in Unspecified specimen by NAA with probe detection	LOINC
723476	SARS-CoV-2 (COVID19) RNA [Presence] in Nasopharynx by NAA with non-probe detection	LOINC
586526	SARS-CoV-2 (COVID19) RNA [Presence] in Nasopharynx by NAA with probe detection	LOINC
757677	SARS-CoV-2 (COVID19) RNA [Presence] in Nose by NAA with probe detection	LOINC
706163	SARS-CoV-2 (COVID19) RNA [Presence] in Respiratory specimen by NAA with probe detection	LOINC
715260	SARS-CoV-2 (COVID19) RNA [Presence] in Saliva (oral fluid) by NAA with probe detection	LOINC
715261	SARS-CoV-2 (COVID19) RNA [Presence] in Saliva (oral fluid) by Sequencing	LOINC
723463	SARS-CoV-2 (COVID19) RNA [Presence] in Serum or Plasma by NAA with probe detection	LOINC
706170	SARS-CoV-2 (COVID19) RNA [Presence] in Unspecified specimen by NAA with probe detection	LOINC
706158	SARS-CoV-2 (COVID19) RNA panel - Respiratory specimen by NAA with probe detection	LOINC
706169	SARS-CoV-2 (COVID19) RNA panel - Unspecified specimen by NAA with probe detection	LOINC
723467	SARS-CoV-2 (COVID19) S gene [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	LOINC
723468	SARS-CoV-2 (COVID19) S gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	LOINC

723465	SARS-CoV-2 (COVID19) S gene [Presence] in Respiratory specimen by NAA with probe detection	LOINC
586519	SARS-CoV-2 (COVID19) S gene [Presence] in Serum or Plasma by NAA with probe detection	LOINC
723466	SARS-CoV-2 (COVID19) S gene [Presence] in Unspecified specimen by NAA with probe detection	LOINC
586517	SARS-CoV-2 (COVID19) whole genome [Nucleotide sequence] in Isolate by Sequencing	LOINC
40218805	Testing for SARS-CoV-2 in CDC laboratory	HCPCS
40218804	Testing for SARS-CoV-2 in non-CDC laboratory	HCPCS

Supporting Table 3. Definitions and codes used for hypertension and other comorbidities

Name	Included Codes
Hyperlipidemia	https://atlas.ohdsi.org/#/concept/432867
Chronic kidney disease	https://atlas.ohdsi.org/#/cohortdefinition/312
Cancer	https://atlas.ohdsi.org/#/cohortdefinition/222
Asthma	https://atlas.ohdsi.org/#/cohortdefinition/218
Dementia	https://atlas.ohdsi.org/#/cohortdefinition/226
Total cardiovascular disease	https://atlas.ohdsi.org/#/cohortdefinition/246
Peripheral vascular disease	https://atlas.ohdsi.org/#/concept/321052

Cerebrovascular disease	https://atlas.ohdsi.org/#/concept/381591
Chronic liver disease	https://atlas.ohdsi.org/#/concept/4212540
Chronic obstructive pulmonary disease	https://atlas.ohdsi.org/#/cohortdefinition/219
Heart disease	https://atlas.ohdsi.org/#/cohortdefinition/231
Hypertension	https://atlas.ohdsi.org/#/cohortdefinition/227
Obesity	https://atlas.ohdsi.org/#/cohortdefinition/224
Type 2 Diabetes Mellitus	https://atlas.ohdsi.org/#/cohortdefinition/311

Supporting Table 4. Prevalence of hypertension among COVID-19 patients in the diagnosed and hospitalised cohorts in the CHARYBDIS Network.

	Diagnosed with COVID-19		Hospitalized with COVID-19	
	N of prevalent cases	% (95% CI)	N of prevalent cases	% (95% CI)
IQVIA-OpenClaims-US	1,245,436	48.3 (48.2-48.4)	384,508	76.5 (76.3-76.6)
OPTUM-EHR-US	66,432	37.4 (37.2-37.7)	18,242	64.1 (63.5-64.6)
VA-OMOP-US	34,093	61.4 (61.0-61.8)	8,996	85.9 (85.2-86.6)

HEALTHVERITY-US	25,405	22.3 (22.0-22.5)	4,512	59.5 (58.4-60.6)
SIDIAP-Spain	21,289	17.4 (17.2-17.6)	5,636	31.0 (30.3-31.6)
CUIMC-US	3,672	43.1 (42.1-44.2)	1,708	65.7 (63.9-67.5)
IQVIA-LPD-France	3,260	19.0 (18.4-19.6)	-	-
CU-AMC-HDC-US	2,461	33.9 (32.8-34.9)	904	63.0 (60.5-65.5)
IQVIA-DA-Germany	2,418	30.3 (29.3-31.3)	-	-
HIRA-South Korea	-	-	1943	25.6 (24.6-26.6)
IQVIA-LPD-Italy	1,618	36.1 (34.6-37.5)	-	-
STARR-OMOP-US	1,246	37.4 (35.8-39.1)	342	55.6 (51.7-59.5)
HMAR-Spain	-	-	594	29.5 (27.5-31.5)
CPRD-UK	756	22.4 (21.0-23.8)	-	-
IPCI-The Netherlands	676	22.2 (20.7-23.7)	-	-

BMJ Open

Characteristics and outcomes of COVID-19 patients with and without prevalent hypertension: a multinational cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-057632.R1
Article Type:	Original research
Date Submitted by the Author:	08-Nov-2021
Complete List of Authors:	<p>Reyes, Carlen; GREMPAL Research Group, Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), and CIBERFes, Universitat Autònoma de Barcelona and Instituto de Salud Carlos III,</p> <p>Pistillo, Andrea ; Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol),</p> <p>Fernández-Bertolín, Sergio; Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol),</p> <p>Recalde, Martina; IDIAP Jordi Gol</p> <p>Roel, Elena; IDIAP Jordi Gol</p> <p>Puente, Diana; IDIAP Jordi Gol, Research</p> <p>Sena, Anthony; Janssen Research and Development Titusville</p> <p>Blacketer, Clair; Janssen Research and Development Titusville</p> <p>Lai, Lana; The University of Manchester, School of Medical Sciences</p> <p>Alshammari, Thamir; King Saud University, Medication Safety Research Chair; Saudi Food and Drug Authority,</p> <p>Ahmed, Waheed-UI-Rahman; University of Oxford Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences</p> <p>Alser, Osaid ; Harvard Medical School, Trauma, Emergency Surgery and Surgical Critical Care</p> <p>Alghoul, Heba; Islamic University of Gaza Faculty of Medicine,</p> <p>Areia, Carlos; University of Oxford, Nuffield Department of Clinical Neurosciences</p> <p>Dawoud, Dalia; National Institute for Health and Care Excellence,</p> <p>Prats-Urbe, Albert; University of Oxford, Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Science</p> <p>Valveny, Neus; TFS health science</p> <p>de Maeztu, Gabriel; IOMED</p> <p>Sorlí Redó, Luisa; Universitat Autònoma de Barcelona</p> <p>Martinez Roldan, Jordi; Hospital del Mar</p> <p>Lopez Montesinos, Inmaculada; IMIM</p> <p>Schilling, Lisa; University of Colorado - Anschutz Medical Campus</p> <p>Golozar, Asieh; Johns Hopkins University Bloomberg School of Public Health</p> <p>Reich, Christian; IQVIA</p> <p>Posada, Jose; Stanford University School of Medicine</p> <p>Shah, Nigam ; Stanford University,</p> <p>You, Seng; Yonsei University College of Medicine, Department of Preventive Medicine</p>

	Lynch, Kristine; Department of Veterans Affairs; The University of Utah School of Medicine DuVall, Scott; Department of Veterans Affairs; The University of Utah School of Medicine Matheny, Michael; VA Tennessee Valley Healthcare System, GRECC; Vanderbilt University Medical Center, Department of Biomedical Informatics Nyberg, Fredrik; University of Gothenburg Sahlgrenska Academy, School of Public Health and Community Medicine, Institute of Medicine, Institute of Medicine Ostropolets, Anna; Columbia University Irving Medical Center Hripcsak, George; Columbia University Irving Medical Center Rijnbeek, P; Erasmus Medical Center, Rotterdam Suchard, MA; University of California Los Angeles, Ryan, Patrick; Janssen Research and Development LLC, Observational Health Data Analytics; Columbia University Irving Medical Center, Department of Biomedical Informatics Kostka, Kristin; IQVIA Duarte-Salles, Talita; Institut de Recerca en Atencio Primaria Jordi Gol,
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	General practice / Family practice
Keywords:	COVID-19, EPIDEMIOLOGY, Hypertension < CARDIOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 1 Characteristics and outcomes of COVID-19 patients with and without prevalent
4
5 2 hypertension: a multinational cohort study
6
7 3
8
9

10 4 Carlen Reyes¹, Andrea Pistillo¹, Sergio Fernández-Bertolín¹, Martina Recalde^{1,2}, Elena
11
12 5 Roel^{1,2}, Diana Puente^{1,2}, Anthony G. Sena^{3,4}, Clair Blacketer^{3,4}, Lana Lai⁵, Thamir M
13
14 6 Alshammari⁶, Waheed-UI-Rahman Ahmed^{7,8}, Osaid Alser⁹, Heba Alghoul¹⁰, Carlos Areia¹¹,
15
16 7 Dalia Dawoud^{12,13}, Albert Prats-Urbe¹⁴, Neus Valveny¹⁵, Gabriel de Maeztu¹⁶, Luisa Sorlí
17
18 8 Redó^{2,17,18}, Jordi Martínez Roldán¹⁹, Inmaculada López Montesinos¹⁷, Lisa M Schilling²⁰,
19
20 9 Asieh Golozar^{21,22}, Christian Reich²³, Jose D. Posada²⁴, Nigam H. Shah²⁴, Seng Chan You²⁵,
21
22 10 Kristine E. Lynch^{26,27}, Scott L. DuVall^{26,27}, Michael E. Matheny^{26,27}, Fredrik Nyberg²⁸, Anna
23
24 11 Ostropolets²⁹, George Hripcsak^{30,31}, Peter R. Rijnbeek³², Mark A. Suchard³³, Patrick Ryan^{3,30},
25
26 12 Kristin Kostka^{23,34}, Talita Duarte-Salles^{1*}
27
28
29
30
31
32

33 14 Affiliations:

- 34
35 15 1- Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i
36
37 16 Gurina (IDIAPJGol), Barcelona, Spain.
38
39
40 17 2- Universitat Autònoma de Barcelona, Spain
41
42
43 18 3- Janssen Research & Development, Titusville, NJ, USA
44
45
46 19 4- Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, The
47
48 20 Netherlands
49
50
51 21 5- School of Medical Sciences, University of Manchester, UK
52
53
54 22 6- College of Pharmacy, Riyadh Elm University Riyadh, Saudi
55
56
57 23 7- Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences,
58
59 24 University of Oxford, Botnar Research Centre, Windmill Road, Oxford, UK.
60

- 1
- 2
- 3 25 8- College of Medicine and Health, University of Exeter, St Luke's Campus, Heavitree
- 4
- 5 26 Road, Exeter, UK
- 6
- 7
- 8 27 9- Massachusetts General Hospital, Harvard Medical School, USA
- 9
- 10 28 10- Faculty of Medicine, Islamic University of Gaza, Palestine
- 11
- 12 29 11- Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK
- 13
- 14 30 12- National Institute for Health and Care Excellence (NICE), London, UK
- 15
- 16
- 17 31 13- Cairo University, Faculty of Pharmacy, Cairo, Egypt
- 18
- 19 32 14- Centre for Statistics in Medicine, NDORMS, University of Oxford, Botnar Research
- 20
- 21 33 Centre, Nuffield Orthopaedic Centre, Windmill Road, Oxford, UK
- 22
- 23
- 24 34 15- Real-World Evidence, TFS, Barcelona, Spain
- 25
- 26 35 16- IOMED, Barcelona, Spain
- 27
- 28 36 17- Department of Infectious Diseases, Hospital del Mar, Institut Hospital del Mar
- 29
- 30 37 d'Investigació Mèdica (IMIM), Barcelona, Spain
- 31
- 32
- 33 38 18- Universitat Pompeu Fabra, Barcelona, Spain
- 34
- 35 39 19- Director of Innovation and Digital Transformation, Hospital del Mar, Barcelona, Spain
- 36
- 37 40 20- University of Colorado Anschutz Medical Campus, Aurora, CO, USA
- 38
- 39
- 40 41 21- Regeneron Pharmaceuticals, Tarrytown, NY, USA
- 41
- 42 42 22- Johns Hopkins Bloomberg School of Public health, NY, USA
- 43
- 44 43 23- Real-World Solutions, IQVIA, Cambridge, MA, USA
- 45
- 46 44 24- Stanford University School of Medicine, Stanford, CA, USA
- 47
- 48 45 25- Department of Preventive Medicine, Yonsei University College of Medicine, Seoul,
- 49
- 50 46 Korea
- 51
- 52 47 26- VA Informatics and Computing Infrastructure, VA Salt Lake City Health Care System,
- 53
- 54 48 Salt Lake City, UT, USA
- 55
- 56
- 57
- 58
- 59
- 60

- 1
2
3 49 27- Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City,
4
5 50 UT, USA
6
7
8 51 28- School of Public Health and Community Medicine, Institute of Medicine, Sahlgrenska
9
10 52 Academy, University of Gothenburg, Gothenburg, Sweden
11
12 53 29- Columbia University Irving Medical Center, New York, USA
13
14 54 30- Department of Biomedical Informatics, Columbia University Irving Medical Center, New
15
16 55 York, NY, USA
17
18 56 31- Medical Informatics Services, NewYork-Presbyterian Hospital, New York, NY, USA
19
20 57 32- Department of Medical Informatics Erasmus University Medical Center, Rotterdam, The
21
22 58 Netherlands
23
24 59 33- Department of Biostatistics, Fielding School of Public Health, University of California,
25
26 60 Los Angeles, USA
27
28 61 34- The OHDSI Center at the Roux Institute, Northeastern University, Portland, ME, USA
29
30
31
32
33
34

35 63 *Corresponding author:

36
37 64 Talita Duarte-Salles

38
39 65 Fundació Institut Universitari per la recerca a L'Atenció Primària de Salut Jordi Gol I Gurina

40
41 66 (IDIAPJGol)

42
43 67 Gran Via Corts Catalanes, 587, àtic

44
45 68 08007 Barcelona-Spain

46
47 69 Tel: +34-93 4824342

48
49 70 Email: tduarte@idiapjgol.org

50
51 71

52
53 72

54
55 73

1
2
3 74 **ABSTRACT**
4

5 75 **Objective:** To characterize patients with and without prevalent hypertension and COVID-19,
6
7
8 76 and to assess their adverse outcomes in both in and outpatients.
9

10 77 **Design and setting:** Retrospective cohort study using 15 healthcare databases (primary and
11
12 78 secondary electronic health care records, insurance and national claims data) from the US,
13
14
15 79 Europe and South Korea, standardized to the Observation Medical Outcomes Partnership
16
17 80 common data model. Data was gathered from 1st March to 31st October 2020.
18
19

20 81 **Participants:** Two non-mutually exclusive cohorts were defined: 1) individuals *diagnosed*
21
22 82 with COVID-19 (*diagnosed cohort*) and 2) individuals *hospitalized* with COVID-19
23
24 83 (*hospitalized cohort*) and stratified by hypertension status. Follow-up was from COVID-19
25
26 84 diagnosis/hospitalization to death, end of the study period, or 30-days.
27
28
29

30 85 **Outcomes:** Demographics, comorbidities, and 30-day outcomes (hospitalization and death
31
32 86 for the *diagnosed cohort* and adverse events and death for the *hospitalized cohort*) were
33
34 87 reported.
35
36
37

38 88 **Results:** We identified 2,851,035 *diagnosed* and 563,708 *hospitalized* patients with COVID-
39
40 89 19. Hypertension was more prevalent in the latter (range (%), 95%CI) across databases 17.4
41
42 90 (17.2-17.6)- 61.4 (61.0-61.8) and 25.6 (24.6-26.6)-85.9 (85.2-86.6). Patients in both cohorts
43
44 91 with hypertension were predominantly >50-year-old and female. Patients with hypertension
45
46 92 were frequently diagnosed with obesity, heart disease, dyslipidaemia, and diabetes.
47
48 93 Compared to patients without hypertension, patients with hypertension, in the COVID-19
49
50 94 *diagnosed cohort*, had more hospitalizations (range 1.3 (0.4-2.2)- 41.1 (39.5-42.7) vs 1.4
51
52 95 (0.9-1.9)-15.9 (14.9-16.9)) and mortality (0.3(0.1-0.5)-18.5 (15.7-21.3) vs 0.2 (0.2-0.2)-11.8
53
54 96 (10.8-12.8)). Patients in the COVID-19 *hospitalized cohort* with hypertension were more
55
56
57
58
59
60

1
2
3 97 likely to have acute respiratory distress syndrome (0.1(0.0-0.2) -65.6 (62.5-68.7) vs 0.1 (0.0-
4
5 98 0.2)-54.7 (50.5-58.9)), arrhythmia (0.5 (0.3-0.7)-45.8 (42.6-49.0) vs 0.4 (0.3-0.5)-36.8 (32.7-
6
7
8 99 40.9)) and increased mortality (1.8 (0.4-3.2)-25.1 (23.0-27.2) vs 0.7 (0.5-0.9)-10.9 (10.4-
9
10
11 100 11.4)) than patients without hypertension.

12
13 101 **Conclusions:** COVID-19 patients with hypertension were more likely to suffer severe
14
15
16 102 outcomes, hospitalizations and deaths compared to those without hypertension.

17
18 103 **KEY WORDS:** COVID-19, Epidemiology, Hypertension

19
20 104 **WORD COUNT:** 3,014

21
22
23 105 **ARTICLE SUMMARY**

24
25 106 **Strengths and limitations of this study**

- 26
27
28 107 1- This study is unique in its approach to characterizing COVID-19 cases across an
29
30 108 international network of healthcare databases, with diverse healthcare systems and
31
32 109 policies, through a comprehensive federated approach.
- 33
34 110 2- This study was carried out using routinely collected clinical practice data, which
35
36 111 confers a great external validity, but also implies a risk of misclassification.
- 37
38 112 3- This study was intentionally descriptive and was deliberately not designed for causal
39
40 113 inference.
- 41
42 114 4- The diagnosed and/or hospitalized cohorts were non-mutually exclusive.
- 43
44 115 5- The data that underpinned this study mostly came from the initial months of the
45
46 116 COVID-19 pandemic and may not be representative of the COVID-19 cases
47
48 117 diagnosed and/or hospitalized during subsequent periods.
- 49
50
51
52
53
54
55
56
57
58
59
60

119 INTRODUCTION

120 As of September 2021, the ongoing pandemic of the coronavirus disease 2019 (COVID-19)
121 has affected over 220 million people and the estimated death toll surpasses the 4,5 million
122 deaths worldwide¹. Hypertension is a common chronic condition that may increase the risk of
123 hospitalizations and adverse outcomes². A higher prevalence of hypertension has been found
124 among COVID-19 patients compared to the general population, which has attracted the
125 attention of researchers³. The characterization of this population at risk is key to be able to
126 design effective preventive strategies that could, improve patient outcomes and reduce the
127 pressure on healthcare systems.

128 To date, observational studies⁴⁻¹⁶, systematic reviews, and meta-analyses have reported an
129 increased risk of progression to severe COVID-19 and increased mortality in patients with
130 hypertension¹⁷⁻²¹. However, these studies, either only included hospitalized patients^{4-13,15-16},
131 leading to a selection bias, or had a small sample size^{6-10,15}, both of which limits the
132 extrapolation of results.

133 Most patients with confirmed SARS-CoV-2 infection, experience mild or moderate
134 symptoms (80%)²² and are predominantly seen as outpatients, therefore a large
135 characterization study including both inpatient and outpatients is needed.

136 This study aims to describe and compare the demographics, baseline comorbidities and 30-
137 day outcomes of individuals with COVID-19 and with and without pre-existing hypertension,
138 in both in and outpatients.

139 MATERIAL AND METHODS

140 Study design, setting, and data sources

141 A multinational, multi-data base cohort study was conducted using data from 1st March to the
142 31st October 2020 included in “The Characterizing Health Associated Risks and Your

1
2
3 143 Baseline Disease In SARS-COV-2” (CHARYBDIS ²³) study. This is a large-scale
4
5 144 multinational cohort study aimed to characterize health-associated risks and baseline diseases
6
7 145 in SARS-COV-2 patients using routinely collected primary care and hospital electronic
8
9 146 health records (EHR), hospital billing, and insurance claims data from the United States
10
11 147 (US), Europe (the Netherlands, Spain, the United Kingdom (UK), Germany, and France) and
12
13 148 Asia (South Korea and China).

14
15
16
17 149 From the databases contributing to CHARYBDIS, only twenty had available information on
18
19 150 pre-existing hypertension and were initially selected. To be included in the study, databases
20
21 151 had to: 1. have at least 140 subjects with prevalent hypertension diagnosed with COVID-19
22
23 152 (necessary to estimate the prevalence of previous conditions or 30-day outcomes with
24
25 153 sufficient precision (confidence interval width of $\pm 5\%$)) and 2. have at least one year of
26
27 154 previous data before the date of COVID-19 diagnosis or hospitalization. Data results for this
28
29 155 paper were extracted on the 21st of January 2021 ²³. Fifteen databases complied with the
30
31 156 aforementioned inclusion criteria. Of these, five had data for outpatients (IQVIA-
32
33 157 Longitudinal Patients Database “LPD” (France), IQVIA-Longitudinal Patients Database
34
35 158 “LPD” (Italy), IQVIA-Disease Analyser “DA” (Germany), Clinical Practice Research
36
37 159 Datalink “CPRD” (UK), Integrated Primary Care Information “IPCI” (the Netherlands), two
38
39 160 had data for in-patients (Health Insurance Review & Assessment Service “HIRA” (South
40
41 161 Korea), Hospital del Mar “HMAR” (Spain)) and eight had both in and out-patient data
42
43 162 (IQVIA-OpenClaims, HEALTHVERITY, Information System for Research in Primary Care
44
45 163 “SIDIAP” (Spain ²⁴), Optum© de-identified Electronic health Record Dataset “OPTUM-
46
47 164 HER” (US), VA-OMOP, University of Colorado Anschutz Medical Campus Health Data
48
49 165 Compass “CUIMC” (US), CU-AMC-HDC, STANford Medicine Research Data Repository
50
51
52
53
54
55
56
57
58
59
60

1
2
3 166 “STARR-OMOP” (US ²⁵). A more detailed description of the included data sources is
4
5 167 available in the Supporting Figure 1 and Table 1.
6
7

8 168 **Study participants and follow-up**

9
10 169 Two non-mutually exclusive cohorts were defined: 1) individuals *diagnosed* with COVID-19
11
12 170 (COVID-19 *diagnosed*) and 2) individuals *hospitalized* with COVID-19 (COVID-19
13
14 171 *hospitalized*). COVID-19 *diagnosed* cohort included individuals with a COVID-19 clinical
15
16 172 diagnosis and/or a SARS-CoV-2 positive test. The COVID-19 *hospitalized* cohort included
17
18 173 patients hospitalized with a COVID-19 clinical diagnosis or positive test 21 days before
19
20 174 admission up to the end of their hospitalization. The codes used to identify COVID-19 cases
21
22 175 are described in more detail in Supporting Table 2. The index date (i.e. cohort start date) was
23
24 176 the date of COVID-19 diagnosis or positive test (whichever occurred first), for the diagnosed
25
26 177 cohort; and the date of hospitalization, for the hospitalized cohort. Cohort participants were
27
28 178 followed from the index date to the earliest of death, the end of the observation period, or 30
29
30 179 days after.
31
32
33
34

35 180 **Baseline characteristics and outcomes of interest**

36
37 181 The hypertension diagnosis, as well as the participants’ sex and age, were gathered at the
38
39 182 index date and identified comorbidities in the year before the index date. Hypertension
40
41 183 diagnosis and comorbidities (asthma, cancer, chronic kidney and liver disease, chronic
42
43 184 obstructive pulmonary disease, dementia, heart disease, hyperlipidaemia, peripheral vascular
44
45 185 disease, type 2 diabetes mellitus, obesity) were ascertained based on the Systematized
46
47 186 Nomenclature of Medicine Current Terminology (SNOMED CT) hierarchy, with all
48
49 187 descendant codes included. We selected and included comorbidities based on their
50
51 188 prevalence in the cohorts of the participating sites and their clinical relevance to the COVID-
52
53 189 19 research field ¹⁷⁻²¹. Clinical epidemiologists generated a list of codes for the identification
54
55 190 of prior medical conditions and outcomes of interest using a web-based integrated platform
56
57
58
59
60

1
2
3 191 (ATLAS tool: <https://atlas.ohdsi.org/>). The definition of the variables can be found in
4
5 192 Supporting Table 3.
6
7
8 193 Our main 30-day outcomes of interest were hospitalization and death for the COVID-19
9
10 194 *diagnosed* cohort, and requirement of intensive services (identified as any record of
11
12 195 mechanical ventilation and/or a tracheostomy and/or extracorporeal membrane oxygenation
13
14 196 procedure), acute respiratory distress syndrome (ARDS), arrhythmia, total cardiovascular
15
16 197 events (ischemic stroke, haemorrhagic stroke, heart failure (heart failure during
17
18 198 hospitalization for the hospitalized cohort), acute myocardial infarction or sudden cardiac
19
20 199 death), sepsis, venous thromboembolism (VTE) and death for the COVID-19 *hospitalized*
21
22 200 cohort.
23

26 201 **Statistical analyses**

28 202 All data were standardized to the Observational Medical Outcomes Partnership (OMOP)
29
30 203 Common Data Model (CDM) ²⁶. A common analytical code for the CHARYBDIS study was
31
32 204 developed for the Observational Health Data Sciences and Informatics (OHDSI) Methods
33
34 205 Library which was run locally in each database. Only aggregate results from each database
35
36 206 were publicly shared. The CHARYBDIS protocol and source code can be found at
37
38 207 <https://github.com/ohdsi-studies/Covid19CharacterizationCharybdis>.
39
40
41 208 Demographics (sex and age categorized in 5-year age bands), comorbidities and 30-day
42
43 209 incidence rates of outcomes were reported as proportions, along with 95% Confidence
44
45 210 Intervals (CI). A minimum of 5 individuals was established to minimize the risk of
46
47 211 identification of patients.
48
49
50 212 All results are reported by cohort, database and by hypertension status (with or without
51
52 213 hypertension).
53
54
55 214 This is a descriptive study and no causal inference is intended. Multivariable regression or
56
57 215 adjustment for confounding was therefore considered out of remit, and not included in our
58
59
60

1
2
3 216 study. We used R version 4.0.3 for data visualization. Before performing these analyses, all
4
5 217 the data partners requested the Institutional Review Board (IRB) or equivalent governance
6
7 218 approval. The full ethics committees' statement is detailed in the ethics statement section. All
8
9 219 data partners consented to the external sharing of the result set on data.ohdsi.org. Consent to
10
11 220 participate was not required as only anonymised retrospective data was used for this study
12
13
14 221 and no patient or GP contact was required.

17 222 **Patient and Public Involvement**

18
19 223 No patient involved

21 224 **RESULTS**

23 225 **Study population**

24
25 226 Overall, 2,851,035 patients diagnosed and 563,708 patients hospitalized with COVID-19
26
27 227 were identified in 15 databases from 8 countries (the US, South Korea, Germany, the
28
29 228 Netherlands, France, Italy, Spain, and the UK). In total, 1,408,762 and 427,385 patients
30
31 229 diagnosed and hospitalized with COVID-19, respectively, had a prior diagnosis of
32
33 230 hypertension (Supporting Table 4). The prevalence of hypertension ranged from 17.4% to
34
35 231 48.3% in the COVID-19 *diagnosed* cohort, and from 25.6% to 85.9% in the COVID-19
36
37 232 *hospitalized cohort*.

40 233 **Baseline characteristics**

41
42 234 The age and sex distribution in the COVID-19 *diagnosed cohort* and in the COVID-19
43
44 235 *hospitalized cohort*, with and without hypertension are represented in Figures 1 and 2
45
46 236 respectively. Overall, in both cohorts, patients with hypertension were older than those
47
48 237 without (higher proportion of patients aged above 50 across all databases). The proportion of
49
50 238 patients *diagnosed* with COVID-19 and hypertension peaked at a younger age (55 to 70 years
51
52 239 old) compared to those *hospitalized* (70 to 80 years old). The proportion of women with
53
54
55
56
57
58
59
60

240 hypertension was greater in the *diagnosed* cohort (8.6 % to 55.6%) than in the *hospitalized*
 241 cohort (4.5% to 56%).

242 **Baseline comorbidities**

243 Figures 3 and 4 reports the proportion of baseline comorbidities of the COVID-19 *diagnosed*
 244 cohort (Figure 3) and COVID-19 *hospitalized* cohort (Figure 4), with and without
 245 hypertension. Patients with hypertension and COVID-19 *diagnosed* or *hospitalized* were
 246 frequently diagnosed with obesity, heart disease, dyslipidaemia, and type 2 diabetes, the
 247 proportion of which, more than double the ones found among patients with COVID-19
 248 without hypertension.

249 **30-day outcomes of interest**

250 Thirty-day outcomes in people with and without hypertension in both the COVID-19
 251 *diagnosed* and/or *hospitalized* cohorts are reported in Tables 1 and 2.

252 Patients with hypertension *diagnosed* with COVID-19 were more likely to be hospitalized
 253 (range 1.3% to 41.1% vs 1.4 to 15.9%) and had increased mortality (range 0.3% to 18.5% vs
 254 0.2% to 11.8%) when compared to those without hypertension (Table 1).

Table 1. Comparison of 30-day outcomes of interest between COVID-19 patients with and without hypertension (HTN), in the COVID-19 diagnosed cohorts in the CHARYBDIS Network, % (95%CI)

Database	HTN	N	30-day outcomes	
			Death	Hospitalization
IQVIA-OpenClaims	With	1,245,436	-	29.6 (29.5-29.7)

(US)				
	Without	1,333,227	-	8.9 (8.9-8.9)
OPTUM-HER (US)	With	6,6432	1.7 (1.6-1.8)	26.4 (26.1-26.7)
	Without	11,1033	0.2 (0.2-0.2)	9.2 (9.0-9.4)
VA-OMOP (US)	With	34,093	5.4 (5.2-5.6)	23.4 (23.0-23.8)
	Without	21,464	0.7 (0.6-0.8)	6.1 (5.8-6.4)
HEALTHVERITY (US)	With	25,405	-	14.6 (14.2-15.0)
	Without	88,768	-	3.1 (3.0-3.2)
SIDIAP (Spain)	With	21,289	9.8 (9.4-10.2)	22.8 (22.2-23.4)
	Without	100,852	3.3 (3.2-3.4)	11.2 (11.0-11.4)
CUIMC (US)	With	3,672	11.8 (10.8-12.8)	41.1 (39.5-42.7)
	Without	4,847	2.0 (1.6-2.4)	15.9 (14.9-16.9)
CU-AMC-HDC (US)	With	2,461	5.9 (5.0-6.8)	35.8 (33.9-37.7)
	Without	4,809	0.7 (0.5-0.9)	11.2 (10.3-12.1)
IQVIA-DA (Germany)	With	2,418	0.3 (0.1-0.5)	-
	Without	5,553	-	-
STARR-OMOP (US)	With	1,246	0.6 (0.2-1.0)	24.6 (22.2-27.0)
	Without	2,082	-	14.0 (12.5-15.5)
CPRD (UK)	With	756	18.5 (15.7-21.3)	-

	Without	2,616	11.8 (10.6-13.0)	-
IPCI (The Netherlands)	With	676	13.6 (11.0-16.2)	1.3 (0.4-2.2)
	Without	2,371	3.1 (2.4-3.8)	1.4 (0.9-1.9)
Note: “-” means information is not available or <5 cases for all databases except for CU-AMC HDC where information is not available for <10 cases.				

258

259 Patients with hypertension *hospitalized* with COVID-19 were more frequently diagnosed of
 260 ARDS (range 0.1 to 65.6% vs 0.1 to 54.7%), cardiac arrhythmia (range 0.5 to 45.8% vs 0.4 to
 261 36.8%), and had increased mortality (range 1.8 to 25.1% vs 0.7 to 10.9%) as compared to
 262 those without hypertension (Table 2).

Table 2. Comparison of 30-days outcomes of interest between COVID-19 patients with and without hypertension (HTN), in the COVID-19 hospitalized cohorts in the CHARYBDIS Network, % (95%CI)

Database	HTN*	N	30-day outcomes						
			VTE†	Death	Cardiac arrhythmia	Sepsis	ARDS‡	Intensive services	Total CVE§
IQVIA-OpenClaims (US)	With	384,508	3.9 (3.8-4.0)	-	15.4 (15.3-15.5)	18.3 (18.2-18.4)	34.8 (34.6-35.0)	9.1 (9.0-9.2)	11.3 (11.2-11.4)
	Without	118,425	3.8 (3.7-3.9)	-	7.2 (7.1-7.3)	15.5 (15.3-15.7)	31.3 (31.0-31.6)	6.4 (6.3-6.5)	4.5 (4.4-4.6)
OPTUM-HER (US)	With	18,242	6.2 (5.9-6.5)	5.1 (4.8-5.4)	31.6 (30.9-32.3)	24.8 (24.2-25.4)	45.7 (45.0-46.4)	14.0 (13.5-14.5)	18.2 (17.6-18.8)
	Without	10,222	4.4 (4.0-4.8)	1.6 (1.4-1.8)	11.1 (10.5-11.7)	15.0 (14.3-15.7)	27.5 (26.6-28.4)	6.3 (5.8-6.8)	4.8 (4.4-5.2)
VA-OMOP (US)	With	8,996	7.3 (6.8-7.8)	15.4 (14.7-16.1)	33.9 (32.9-34.9)	20.0 (19.2-20.8)	43.9 (42.9-44.9)	17.1 (16.3-17.9)	21.0 (20.2-21.8)
	Without	1,475	6.9 (5.6-8.2)	7.6 (6.2-9.0)	16.8 (14.9-18.7)	16.2 (14.3-18.1)	39.6 (37.1-42.1)	11.2 (9.6-12.8)	7.3 (6.0-8.6)
HEALTHVERITY (US)	With	4,512	3.6 (3.1-4.1)	-	14.8 (13.8-15.8)	16.5 (15.4-17.6)	26.7 (25.4-28.0)	6.1 (5.4-6.8)	11.9 (11.0-12.8)
	Without	3,069	3.9 (3.2-4.6)	-	6.8 (5.9-7.7)	12.5 (11.3-13.7)	23.9 (22.4-25.4)	4.9 (4.1-5.7)	5.6 (4.8-6.4)

SIDIAP (Spain)	With	5,636	1.0 (0.7-1.3)	15.4 (14.5-16.3)	0.5 (0.3-0.7)	-	0.1 (0.0-0.2)	-	0.9 (0.7-1.1)
	Without	12,566	1.1 (0.9-1.3)	10.9 (10.4-11.4)	0.4 (0.3-0.5)	0.0 (0.0-0.0)	0.1 (0.0-0.2)	-	0.5 (0.4-0.6)
CUIMC (US)	With	1,708	3.9 (3.0-4.8)	25.1 (23.0-27.2)	12.1 (10.6-13.6)	6.1 (5.0-7.2)	16.0 (14.3-17.7)	2.2 (1.5-2.9)	8.1 (6.8-9.4)
	Without	892	3.6 (2.4-4.8)	10.2 (8.2-12.2)	4.7 (3.3-6.1)	5.3 (3.8-6.8)	17.8 (15.3-20.3)	1.8 (0.9-2.7)	3.8 (2.5-5.1)
CU-AMC HDC (US)	With	904	11.4 (9.3-13.5)	14.9 (12.6-17.2)	45.8 (42.6-49.0)	34.2 (31.1-37.3)	65.6 (62.5-68.7)	28.3 (25.4-31.2)	19.8 (17.2-22.4)
	Without	530	6.0 (4.0-8.0)	6.0 (4.0-8.0)	36.8 (32.7-40.9)	27.4 (23.6-31.2)	54.7 (50.5-58.9)	15.5 (12.4-18.6)	5.7 (3.7-7.7)
HIRA (South Korea)	With	1,943	0.7 (0.3-1.1)	7.7 (6.5-8.9)	4.4 (3.5-5.3)	5.3 (4.3-6.3)	2.6 (1.9-3.3)	4.9 (3.9-5.9)	10.0 (8.7-11.3)
	Without	5,656	NC	0.7 (0.5-0.9)	0.7 (0.5-0.9)	3.1 (2.6-3.6)	0.5 (0.3-0.7)	0.6 (0.4-0.8)	4.7 (4.1-5.3)
STARR-OMOP (US)	With	342	2.0 (0.5-3.5)	1.8 (0.4-3.2)	22.2 (17.8-26.6)	9.9 (6.7-13.1)	12.6 (9.1-16.1)	9.1 (6.1-12.1)	16.4 (12.5-20.3)
	Without	273	NC	-	6.6 (3.7-9.5)	7.0 (4.0-10.0)	11.4 (7.6-15.2)	5.5 (2.8-8.2)	-
HMAR (Spain)	With	594	3.2 (1.8-4.6)	14.3 (11.5-17.1)	23.1 (19.7-26.5)	1.9 (0.8-3.0)	12.6 (9.9-15.3)	13.5 (10.8-16.2)	12.1 (9.5-14.7)
	Without	1,417	2.6 (1.8-3.4)	3.9 (2.9-4.9)	6.6 (5.3-7.9)	0.7 (0.3-1.1)	7.3 (5.9-8.7)	6.6 (5.3-7.9)	2.2 (1.4-3.0)
Note: “-” means information is not available or <5 cases for all databases except for CU-AMC HDC where information is not available for <10 cases.									

1
2
3 * hypertension; †: Venous thromboembolic (pulmonary embolism and deep vein thrombosis) events; ‡: Acute respiratory distress syndrome; §: cardiovascular disease
4 events (ischemic stroke, haemorrhagic stroke, heart failure (heart failure during hospitalization for the hospitalized cohort), acute myocardial infarction or sudden cardiac
5 death)
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

For peer review only

1
2
3 **264 DISCUSSION**
4

5 265 This large multinational, multi-database cohort study, reports a greater prevalence of
6
7 266 hypertension among patients *hospitalized* with COVID-19 compared to those *diagnosed* with
8
9
10 267 COVID-19. Patients with hypertension diagnosed and/or hospitalized with COVID-19 were
11
12 268 frequently diagnosed with obesity, heart disease, dyslipidaemia, and type 2 diabetes at
13
14 269 baseline, compared to those without hypertension. They were also more likely to experience
15
16 270 adverse outcomes including death and hospitalizations (in the COVID-19 *diagnosed cohort*)
17
18 271 and cardiac arrhythmia, ARDS and death (in the COVID-19 *hospitalized cohort*) than
19
20 272 patients without hypertension.
21

22
23 273 This is the first large multinational study that characterizes both in and out-patients with
24
25 274 COVID-19, with and without prevalent hypertension. Hypertension was more prevalent in
26
27 275 hospitalized patients compared to those diagnosed with COVID-19 (range from 25.6% to
28
29 276 85.9% vs 17.4 to 61.4% respectively). The observed variability between databases is similar
30
31 277 to previous reports, where prevalence's ranged from 28.8%⁷ to 60%¹⁵.
32

33 278 However, these results should be put into context given that our highest rate (in both COVID-
34
35 279 19 *diagnosed* and COVID-19 *hospitalized*) was observed in the VA-OMOP database from
36
37 280 the US Department of Veterans Affairs (mostly men of older age).
38

39
40 281 As in the general population with hypertension²⁷, patients with hypertension diagnosed with
41
42 282 COVID-19 in this study were more frequently diagnosed with heart disease or type 2 diabetes
43
44 283 at baseline, than individuals without hypertension. These results are similar to what has been
45
46 284 previously published, where patients with hypertension and COVID-19 also reported a higher
47
48 285 prevalence of diabetes mellitus^{6,8,12}, cardiovascular diseases (other than hypertension)^{8,12},
49
50 286 and chronic kidney disease⁸ compared to those without hypertension. This study further
51
52 287 expands these previous findings identifying these same comorbidities in the out-patients
53
54
55
56
57
58
59
60

1
2
3 288 diagnosed with COVID-19 and adds obesity and dyslipidaemia to the list of conditions more
4
5
6 289 frequently found among patients with COVID-19 and hypertension compared to those
7
8 290 without hypertension. The higher prevalence of comorbid conditions found in this study
9
10
11 291 among patients with hypertension *hospitalized* with COVID-19 compared to patients with
12
13 292 hypertension *diagnosed* with COVID-19 suggests a poorer baseline health status.
14
15
16 293 Patients with hypertension *hospitalized* with COVID-19 were more likely to have worse
17
18 294 disease progression with higher rates of ARDS (Prevalence per cent change (PC) between
19
20 295 patients with and without hypertension ranging from -1.8% to 18.2%), more cardiac
21
22 296 arrhythmia (PC ranging from 0.1% to 20.5%) and increased mortality (PC ranging from 3.5%
23
24 297 to 14.9%). Previous studies have documented poorer clinical outcomes in patients with
25
26 298 hypertension hospitalized with COVID-19 (including ARDS) ^{8, 12, 14, 19}, the need for
27
28 299 mechanical ventilation, admission to intensive care units ^{6, 13, 19} or an increased mortality ^{4,7,11-}
29
30 300 ^{13, 19}. This study further showed that patients with hypertension *diagnosed* with COVID-19
31
32 301 were more likely to experience hospitalizations (PC between patients with and without
33
34 302 hypertension ranging from -0.1% to 25.6%), and deaths (PC from 1.5% to 10.5%).
35
36
37 303 These results highlight the importance of considering hypertension as a possible risk factor in
38
39 304 the overall population *diagnosed* and not only in those *hospitalized* with COVID-19. It also
40
41 305 adds to the current literature cardiac arrhythmia and cardiovascular diseases (other than
42
43 306 hypertension) to the list of adverse outcomes more frequently diagnosed among patients with
44
45 307 hypertension hospitalized with COVID-19 compared to those without hypertension.
46
47
48 308 This study has several strengths. This is the largest cohort study on individuals with
49
50 309 hypertension who were *diagnosed* and/or *hospitalized* with COVID-19 to date. It provides
51
52 310 novel insight into the characterization of patients *diagnosed* with COVID-19 and confers a
53
54 311 greater external validity of its results compared to what has been published up to date (only
55
56 312 *hospitalized* patients). It is also unique in its approach to characterizing COVID-19 cases
57
58
59
60

1
2
3 313 across an international network of healthcare databases, with diverse healthcare systems and
4
5 314 policies, through a comprehensive federated approach, allowing the analysis of 15 databases
6
7
8 315 without sharing patient identifiable data, hence respecting the patients' confidentiality at all
9
10 316 times.

11
12 317 We recognize there are limitations to our approach. First, this study was intentionally
13
14 318 descriptive and was deliberately not designed for causal inference. The observed differences
15
16
17 319 between groups (eg. with versus without hypertension) should therefore not be interpreted as
18
19 320 causal effects. Our patients were analysed depending on if they were *diagnosed* and/or
20
21 321 *hospitalized* with COVID-19 according to database registration procedures, however,
22
23 322 variations could have occurred during the processes by which patients were screened, tested,
24
25 323 admitted, and registered across time and the databases. Additionally, the diagnosed and/or
26
27 324 hospitalized cohorts were non-mutually exclusive, and therefore could be patients in the
28
29 325 diagnosed cohort who were also hospitalized and vice versa.

30
31
32
33 326 This study was carried out using data recorded in routine clinical practice based on EHRs
34
35 327 and/or claims, therefore, data could be incomplete or be erroneous, leading to potential
36
37 328 misclassification. We have therefore selectively reported database-specific outcomes to
38
39 329 minimize the impact of incompleteness. Differential reporting in databases is likely due to
40
41 330 different coding practices, different primary and secondary level data availability, as well as
42
43 331 variability in disease severity, with milder/less symptomatic cases more likely being only
44
45 332 diagnosed, and more severe ones hospitalized. Finally, the data that underpinned this study
46
47 333 mostly came from the initial months of the COVID-19 pandemic and may not be
48
49 334 representative of the COVID-19 cases diagnosed and/or hospitalized during subsequent
50
51 335 periods.

52
53
54
55
56 336 **CONCLUSIONS**
57
58
59
60

1
2
3 337 COVID-19 patients with hypertension are more likely to have comorbidities, experience
4
5 338 more severe outcomes including hospitalizations and deaths (among outpatients with
6
7 339 COVID-19) and experience more ARDS and deaths (among inpatients' with COVID-19)
8
9 340 compared with patients without hypertension.
10
11

12 341

14 342 **FIGURE LEGENDS**

16
17 343 **Figure 1. Comparison of the age and sex distribution in patients with a COVID-19**
18
19 344 **diagnosis with and without hypertension in the CHARYBDIS Network, %.** Colour Red=
20
21 345 with hypertension, Green= without hypertension.
22

23
24 346 **Figure 2. Comparison of the age and sex distribution in patients with a COVID-19**
25
26 347 **hospitalization with and without hypertension in the CHARYBDIS Network, %.** Colour
27
28 348 Red=with hypertension, Colour Green=without hypertension.
29

30
31 349 **Figure 3. Comorbidities at baseline among patients with a COVID-19 diagnosis with**
32
33 350 **and without hypertension in the CHARYBDIS Network, %.** Colour Red=with
34
35 351 hypertension, Colour Green=without hypertension.
36

37
38 352 **Figure 4. Comorbidities at baseline among patients with a COVID-19 hospitalization**
39
40 353 **with and without hypertension in the CHARYBDIS Network, %.** Colour Red=with
41
42 354 hypertension, Colour Green=without hypertension.
43

44 355

46 356 **CONTRIBUTORSHIP STATEMENT**

47
48
49 357 CR, AGS, CA, APU, AG, FN, AO, GH, PRR, KK, TDS, KEL, SLD, MR, ER, SFB and AP
50
51 358 provided substantial contributions to the conception or design, analysis, and interpretation of
52
53 359 data for the work. CR, AGS, CA, APU, AG, FN, AO, GH, PRR, KK, TDS, KEL, SLD, MR,
54
55 360 ER, SFB, AP, DP, NV, GdeM, LSR, JMR, ILM, NHS, PRy, MAS, MEM, CB, LL, TMA, W-
56
57 361 U-RA, OA, HA, DD drafted or revised the manuscript critically for important intellectual
58
59
60

1
2
3 362 content. All authors approved the final version of the manuscript and CR, AGS, CA, APU,
4
5 363 AG, FN, AO, GH, PRR, KK, TDS, LL, TMA, W-U-RA, OA, HA, DD, LMS, CRei, JDP,
6
7 364 SCY agreed to be accountable for all aspects of the work (KEL and SLD only for VA data) in
8
9 365 ensuring that questions related to the accuracy or integrity of any part of the work are
10
11 366 appropriately investigated and resolved.
12
13
14
15 367

16 368 **COMPETING INTERESTS STATEMENT**

17
18
19 369 SLDV reports grants from Anolinx; MS, reports grants from US National Institutes of Health,
20
21 370 grants from Department of Veterans Affairs, during the conduct of the study; grants from
22
23 371 IQVIA, personal fees from Janssen Research and Development, grants from US Food and
24
25 372 Drug Administration, personal fees from Private Health Management, outside the submitted
26
27 373 work LLC, grants from Astellas Pharma, Inc, grants from AstraZeneca Pharmaceuticals LP,
28
29 374 grants from Boehringer Ingelheim International GmbH, grants from Celgene Corporation,
30
31 375 grants from Eli Lilly and Company, grants from Genentech Inc., grants from Genomic
32
33 376 Health, Inc., grants from Gilead Sciences Inc., grants from GlaxoSmithKline PLC, grants
34
35 377 from Innocrin Pharmaceuticals Inc., grants from Janssen Pharmaceuticals, Inc., grants from
36
37 378 Kantar Health, grants from Myriad Genetic Laboratories, Inc., grants from Novartis
38
39 379 International AG, grants from Parexel International Corporation through the University of
40
41 380 Utah or Western Institute for Veteran Research, outside the submitted work; GH, reports
42
43 381 grants from NIH, during the conduct of the study; grants from Janssen Research, outside the
44
45 382 submitted work; FN, reports that Until 2019 was an employee of AstraZeneca and holds
46
47 383 some AstraZeneca shares, outside the submitted work; KK, reports personal fees from
48
49 384 National Institutes of Health, outside the submitted work, and at the time of data analysis and
50
51 385 initial drafting of the manuscript, KK was an employee of IQVIA Inc; CR reports he is an
52
53 386 employee of IQVIA Inc; GdM is Employee of IOMED; NV is an Employee of TFS; AGS
54
55
56
57
58
59
60

1
2
3 387 reports personal fees from Janssen R&D, outside the submitted work and full time employee
4
5 388 of Janssen R&D and is a Johnson and Johnson shareholder; CB reports personal fees from
6
7 389 Janssen R&D, outside the submitted work and is a full time employee of Janssen R&D and is
8
9 a Johnson and Johnson shareholder; JDP reports grants from National Library of Medicine,
10
11 390 during the conduct of the study; AG is an employee of Regeneron Pharmaceuticals and
12
13 391 reports stocks from Regeneron Pharmaceuticals. PR reports having received research group
14
15 392 grants from Innovative Medicine Initiative and Janssen Research and Development; MS
16
17 393 reports grants from US National Institutes of Health, grants from Department of Veterans
18
19 394 Affairs, during the conduct of the study; grants from IQVIA, personal fees from Janssen
20
21 395 Research and Development, grants from US Food and Drug Administration, personal fees
22
23 396 from Private Health Management, outside the submitted work; PR, reports and is an
24
25 397 employee of Janssen Research and Development and shareholder of Johnson & Johnson; ER,
26
27 398 SFB, NHS, LMS, DP, SCY, MR, APU, HA, KEL, MM, AO, CA, CR, TDS, TMA, OA, W-
28
29 399 U-RA, ILM, JMR, LSR, DD, LYHL, AP, have nothing to declare. The views expressed are
30
31 400 those of the authors and do not necessarily represent the views or policy of the Department of
32
33 401 Veterans Affairs or the United States Government. No other relationships or activities could
34
35 402 appear to have influenced the submitted work.
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

405 **FUNDING STATEMENT**

406 This work was supported by several funders as follows; The European Health Data &
407 Evidence Network received funding from the Innovative Medicines Initiative 2 Joint
408 Undertaking (JU) under grant agreement No 806968. The JU received support from the
409 European Union's Horizon 2020 research and innovation programme and EFPIA. This
410 research received partial support from the National Institute for Health Research (NIHR)
411 Oxford Biomedical Research Centre (BRC), US National Institutes of Health (R01

1
2
3 412 LM006910), US Department of Veterans Affairs, the Health Department from the Generalitat
4
5 413 de Catalunya with a grant for research projects on SARS-CoV-2 and COVID-19 disease
6
7 414 organized by the Direcció General de Recerca i Innovació en Salut, Janssen Research &
8
9 415 Development, TFS, IOMED and IQVIA. The University of Oxford received funding related
10
11 416 to this work from the Bill & Melinda Gates Foundation (Investment ID INV-016201 and
12
13 417 INV-019257). TFS received funding related to this work from the University of Oxford. This
14
15 418 work was also supported with funding, [resources, and facilities] of the Department of
16
17 419 Veterans Affairs (VA) Informatics and Computing Infrastructure (VINCI), VA HSR RES 13-
18
19 420 457. No funders had a direct role in this study. The views and opinions expressed are those of
20
21 421 the authors and do not necessarily reflect those of the Clinician Scientist Award programme,
22
23 422 NIHR, Department of Veterans Affairs or the United States Government, NHS, or the
24
25 423 Department of Health, England.
26
27
28
29
30
31
32

33 425 **DATA SHARING STATEMENT**

34
35 426 Open Science is a guiding principle within OHDSI. As such, we provide unfettered access to
36
37 427 all open-source analysis tools employed in this study via
38
39 428 <https://github.com/ohdsi-studies/Covid19CharacterizationCharybdis>, as well as all data and
40
41 429 results artefacts that do not include patient-level health information via
42
43 430 <https://data.odhsi.org/Covid19CharacterizationCharybdis/>. Data partners contributing to this
44
45 431 study remain custodians of their individual patient-level health information and hold either
46
47 432 IRB exemption or approval for participation.
48
49
50

51 433

52 434 **ACKNOWLEDGEMENTS**

53
54 435 We would like to acknowledge the patients who suffered from or died of this devastating
55
56 436 disease, and their families and carers. We also thank the healthcare professionals involved in
57
58
59
60

1
2
3 437 the management of COVID-19 during these challenging times, from primary care to intensive
4
5 438 care units. The authors appreciate the Korean Health Insurance Review and Assessment
6
7 439 Service for providing data.

8
9
10 440 We also thank the database curation teams around the world including the COVIDMAR
11
12 441 Group (JPHorcajada, R.Güerri, J.Villar, M.Montero, S.Gómez-Zorrilla, M.Arenas-Miras,
13
14 442 J.Gómez-Junyent, I.Arrieta, E.Sendra, S.Castañeda, E.Letang, I.Pelegrín, A.Rial,
15
16 443 J.Rodríguez, C.Gimenez, J.Soldado, E.García).

17
18
19 444 We also thank the important contribution to this work of Dr Daniel Prieto-Alhambra.

20
21
22 445

23 24 446 **ETHICS STATEMENT**

25
26 447 Before performing these analyses, all the data partners received Institutional Review Board
27
28 448 (IRB) approval or exemption. STARR-OMOP had approval from IRB Panel #8 (RB-53248)
29
30 449 registered to Leland Stanford Junior University under the Stanford Human Research
31
32 450 Protection Program (HRPP). The use of VA-OMOP data was reviewed by the Department of
33
34 451 Veterans Affairs Central IRB, was determined to meet the criteria for exemption under
35
36 452 Exemption Category 4(3), and approved for Waiver of HIPAA Authorization. The use of
37
38 453 SIDIAP was approved by the Clinical Research Ethics Committee of the IDIAPJGol (project
39
40 454 code: 20/070-PCV). The use of CPRD was approved by the Independent Scientific Advisory
41
42 455 Committee (ISAC) (protocol number 20_059RA2). The use of the CUIMC database was
43
44 456 approved by the Columbia University Institutional Review Board as an OHDSI network
45
46 457 study (IRB-AAA07805). The use of HMAR was approved by the Parc de Salut Mar Clinical
47
48 458 Research Ethics Committee (Comité de Ética de la Investigación con medicamentos del Parc
49
50 459 de Salut MAR, IRB-2020/9183). The use of HIRA database was approved by the IRB of
51
52 460 Ajou University ('AJIRB-MED-EXP-20-061'). The Colorado Multiple Institutional Review
53
54 461 Board, CB F490University of Colorado, Anschutz Medical Campus extended an exemption
55
56
57
58
59
60

1
2
3 462 of IRB certificate on the 17th of November 2020 for the use of the CU-AMC-HDC data for
4
5 463 this study. Moreover, given that this study only used de-identified data with no transmission
6
7 464 of patient-level information at any time during the analysis and that all data reported was
8
9 465 aggregated and no identification of individual patients or physicians was possible, some
10
11 466 databases (IQVIA Open Claims, IQVIA DA Germany, IQVIA LPD France, IQVIA LPD
12
13 467 Italy, IPCI) deemed this study as being not human subject research and no further approval
14
15 468 was necessary. Furthermore, The New England Institutional Review Board of Janssen
16
17 469 Research & Development (Raritan, NJ) has determined that studies conducted on licensed
18
19 470 copies of Optum EHR and HealthVerity are exempt from study-specific IRB review, as these
20
21 471 studies do not qualify as human subject's research.
22
23
24

25 472 REFERENCES

- 26
27
28 473 1- Weekly Operational Update on COVID-19-6 Sep 2021 [internet]. WHO [cited 9th
29
30 474 September 2021]. Available from [https://www.who.int/publications/m/item/weekly-](https://www.who.int/publications/m/item/weekly-operational-update-on-covid-19---6-september-2021)
31
32 475 [operational-update-on-covid-19---6-september-2021](https://www.who.int/publications/m/item/weekly-operational-update-on-covid-19---6-september-2021).
33
34
35 476 2- Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020
36
37 477 International Society of Hypertension global hypertension practice guidelines. *J Hypertens.*
38
39 478 2020;38:982-1004.
40
41
42 479 3-Cook TM. The importance of hypertension as a risk factor for severe illness and mortality
43
44 480 in COVID-19. *Anaesthesia.* 2020;75:976-977.
45
46
47 481 4-Gupta S, Hayek SS, Wang W, Chan L, Mathews KS, Melamed ML, et al. Factors
48
49 482 Associated With Death in Critically Ill Patients With Coronavirus Disease 2019 in the US.
50
51 483 *JAMA Intern Med.* 2020;180:1–12.
52
53
54 484 5-Jiménez E, Fontán-Vela M, Valencia J, Fernandez-Jimenez I, Álvaro-Alonso EA,
55
56 485 Izquierdo-García E, et al. Characteristics, complications and outcomes among 1549 patients
57
58
59
60

- 1
2
3 486 hospitalised with COVID-19 in a secondary hospital in Madrid, Spain: a retrospective case
4
5
6 487 series study. *BMJ Open*. 2020;10:e042398.
7
8 488 6-Huang S, Wang J, Liu F, Liu J, Cao G, Yang C, et al. COVID-19 patients with
9
10 489 hypertension have more severe disease: a multicenter retrospective observational study.
11
12
13 490 *Hypertens Res*. 2020;43:824-831.
14
15
16 491 7-Park BE, Lee JH, Park HK, Kim HN, Jang SY, Bae MH, et al. Impact of Cardiovascular
17
18 492 Risk Factors and Cardiovascular Diseases on Outcomes in Patients Hospitalized with
19
20
21 493 COVID-19 in Daegu Metropolitan City. *J Korean Med Sci*. 2021;36:e15.
22
23
24 494 8- Yao Q, Ni J, Hu TT, Cai ZL, Zhao JH, Xie QW, et al. Clinical characteristics and
25
26 495 outcomes in coronavirus disease 2019 (COVID-19) patients with and without hypertension: a
27
28 496 retrospective study. *Rev Cardiovasc Med*. 2020;21:615-625.
29
30
31 497 9- Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for
32
33 498 mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.
34
35
36 499 *Lancet*. 2020;395(10229):1054-1062.
37
38
39 500 10-Wang Y, Lu X, Li Y, Chen H, Chen T, Su N, et al. Clinical Course and Outcomes of 344
40
41 501 Intensive Care Patients with COVID-19. *Am J Respir Crit Care Med*. 2020;201:1430-1434.
42
43
44 502 11-Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline
45
46 503 Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to
47
48 504 ICUs of the Lombardy Region, Italy. *JAMA*. 2020;323:1574-1581.
49
50
51 505 12-Gao C, Cai Y, Zhang K, Zhou L, Zhang Y, Zhang X, et al. Association of hypertension
52
53 506 and antihypertensive treatment with COVID-19 mortality: a retrospective observational
54
55
56 507 study. *Eur Heart J*. 2020;41:2058-2066.
57
58
59
60

- 1
2
3 508 13- Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its
4
5
6 509 impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J*.
7
8 510 2020;55:2000547.
9
10
11 511 14- Ji W, Huh K, Kang M, Hong J, Bae GH, Lee R, et al. Effect of Underlying Comorbidities
12
13 512 on the Infection and Severity of COVID-19 in Korea: a Nationwide Case-Control Study. *J*
14
15 513 *Korean Med Sci*. 2020;35:e237.
16
17
18 514 15- Chilimuri S, Sun H, Alemam A, Mantri N, Shehi E, Tejada J, et al. Predictors of
19
20 515 Mortality in Adults Admitted with COVID-19: Retrospective Cohort Study from New York
21
22 516 City. *West J Emerg Med*. 2020;21:779-784.
23
24
25 517 16- Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al.
26
27 518 Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized
28
29 519 With COVID-19 in the New York City Area. *JAMA*. 2020;323:2052-2059. Erratum in:
30
31 520 *JAMA*. 2020;323:2098.
32
33
34 521 17-Dorjee K, Kim H, Bonomo E, Dolma R. Prevalence and predictors of death and severe
35
36 522 disease in patients hospitalized due to COVID-19: A comprehensive systematic review and
37
38 523 meta-analysis of 77 studies and 38,000 patients. *PLoS One*. 2020;15:e0243191.
39
40
41 524 18-Javanmardi F, Keshavarzi A, Akbari A, Emami A, Pirbonyeh N. Prevalence of underlying
42
43 525 diseases in dead cases of COVID-19: A systematic review and meta-analysis. *PLoS One*.
44
45 526 2020;15:e0241265.
46
47
48 527 19-Pranata R, Lim MA, Huang I, Raharjo SB, Lukito AA. Hypertension is associated with
49
50 528 increased mortality and severity of disease in COVID-19 pneumonia: A systematic review,
51
52 529 meta-analysis and meta-regression. *J Renin Angiotensin Aldosterone Syst*.
53
54 530 2020;21:1470320320926899.
55
56
57
58
59
60

- 1
2
3 531 20- Silverio A, Di Maio M, Citro R, Esposito L, Iuliano G, Bellino M, et al. Cardiovascular
4
5
6 532 risk factors and mortality in hospitalized patients with COVID-19: systematic review and
7
8 533 meta-analysis of 45 studies and 18,300 patients. *BMC Cardiovasc Disord.* 2021;21:23.
9
10
11 534 21- Moazzami B, Chaichian S, Kasaeian A, Djalalinia S, Akhlaghdoust M, Eslami M, et al.
12
13 535 Metabolic risk factors and risk of Covid-19: A systematic review and meta-analysis. *PLoS*
14
15 536 *One.* 2020;15:e0243600.
17
18 537 22- Baj J, Karakuła-Juchnowicz H, Teresiński G, Buszewicz G, Ciesielka M, Sitarz E, et al.
19
20 538 COVID-19: Specific and Non-Specific Clinical Manifestations and Symptoms: The Current
21
22 539 State of Knowledge. *J Clin Med.* 2020;9:1753.
23
24
25 540 23- Prieto-Alhambra D, Kostka K, Duarte-Salles T, Prats-Uribe A, Sena A, Pistillo A, et al.
26
27 541 Unraveling COVID-19: a large-scale characterization of 4.5 million COVID-19 cases using
28
29 542 CHARYBDIS. *Res Sq [Preprint].* 2021:rs.3.rs-279400.
30
31
32 543 24- García-Gil M del M, Hermosilla E, Prieto-Alhambra D, Fina F, Rosell M, Ramos R, et al.
33
34 544 Construction and validation of a scoring system for the selection of high-quality data in a
35
36 545 Spanish population primary care database (SIDIAP). *Inform Prim Care.* 2011; 19(3): 135–45
37
38 546 25-Datta S, Posada J, Olson G, Li W, O'Reilly C, Balraj D, et al. A new paradigm for
39
40 547 accelerating clinical data science at Stanford Medicine. *arXiv:2003.10534*
41
42
43 548 26-Voss EA, Makadia R, Matcho A, Ma Q, Knoll C, Schuemie M, et al. Feasibility and
44
45 549 utility of applications of the common data model to multiple, disparate observational health
46
47 550 databases. *J Am Med Inform Assoc.* 2015;22:553-64.
48
49
50 551 27-Tsimihodimos V, Gonzalez-Villalpando C, Meigs JB, Ferrannini E. Hypertension and
51
52 552 Diabetes Mellitus: Coprediction and Time Trajectories. *Hypertension.* 2018;71:422-428.
53
54
55 553
56
57 554
58
59
60

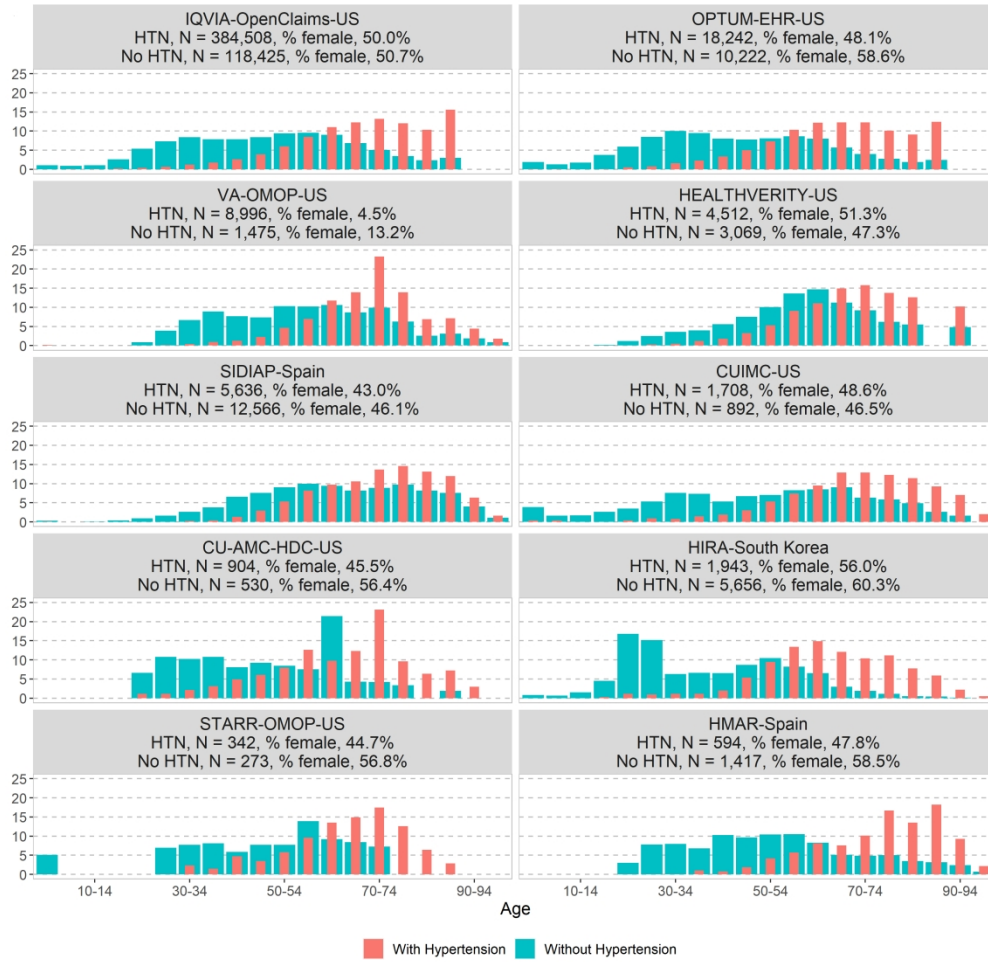


Figure 1. Comparison of the age and sex distribution in patients with a COVID-19 diagnosis with and without hypertension in the CHARYBDIS Network, %. Colour Red= with hypertension, Green= without hypertension.

729x710mm (118 x 118 DPI)

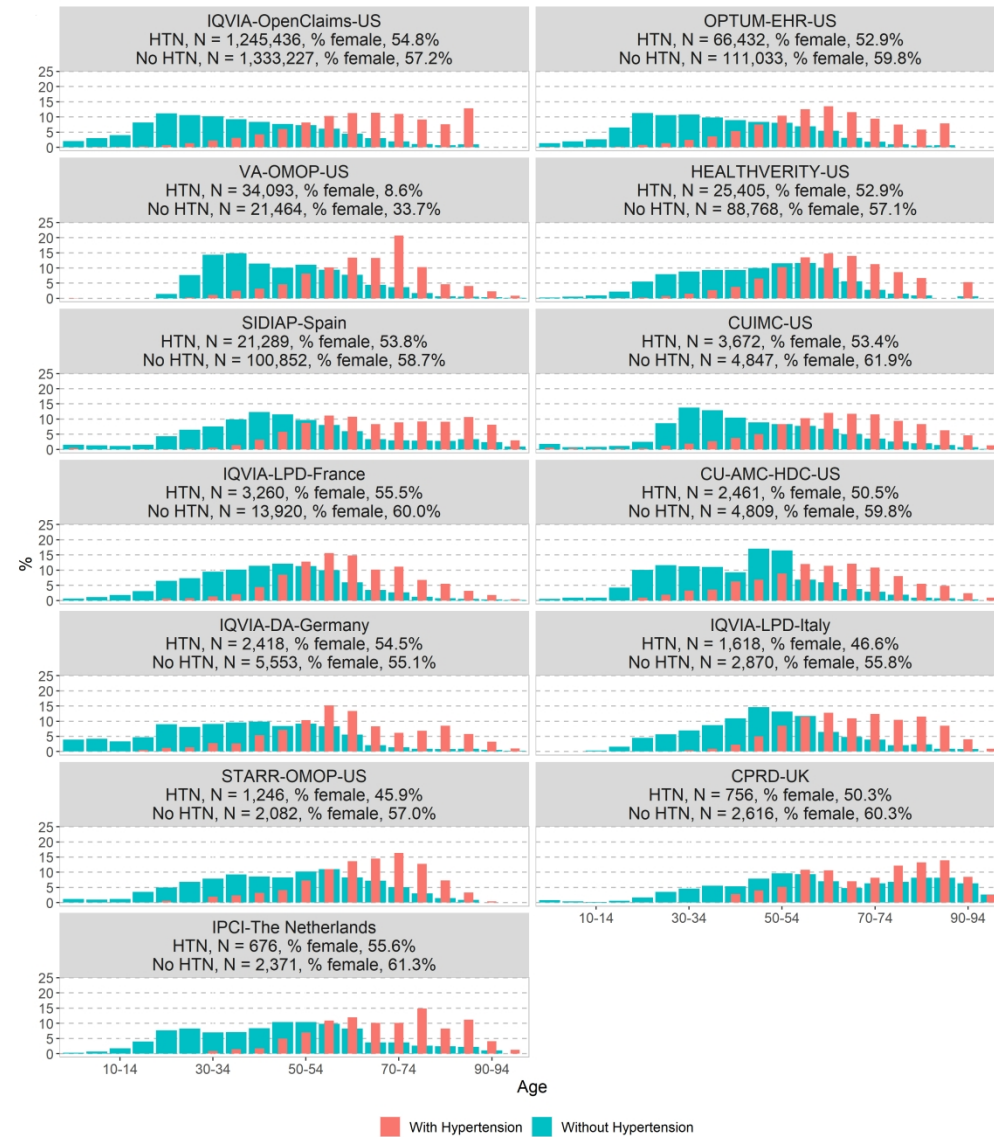


Figure 2. Comparison of the age and sex distribution in patients with a COVID-19 hospitalization with and without hypertension in the CHARYBDIS Network, %. Colour Red=with hypertension, Colour Green=without hypertension.

729x839mm (118 x 118 DPI)

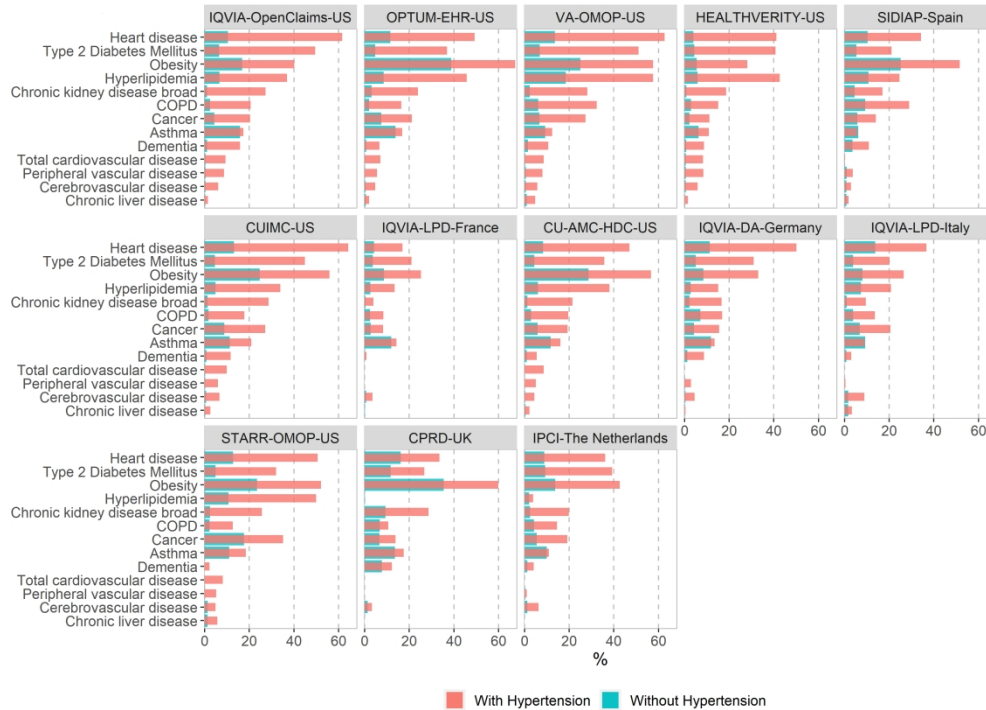


Figure 3. Comorbidities at baseline among patients with a COVID-19 diagnosis with and without hypertension in the CHARYBDIS Network, %. Colour Red=with hypertension, Colour Green=without hypertension.

710x516mm (118 x 118 DPI)

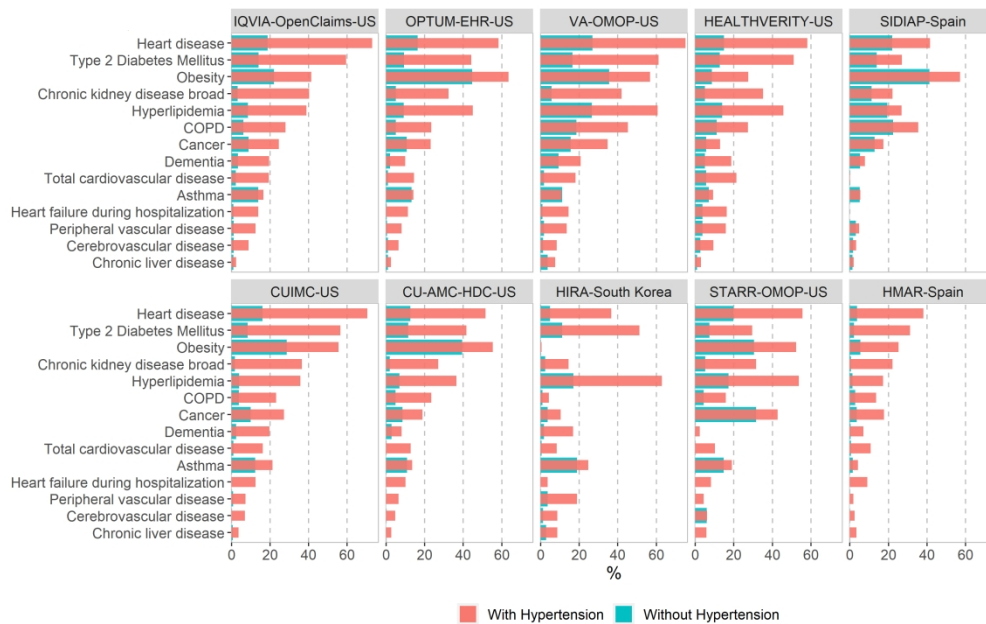
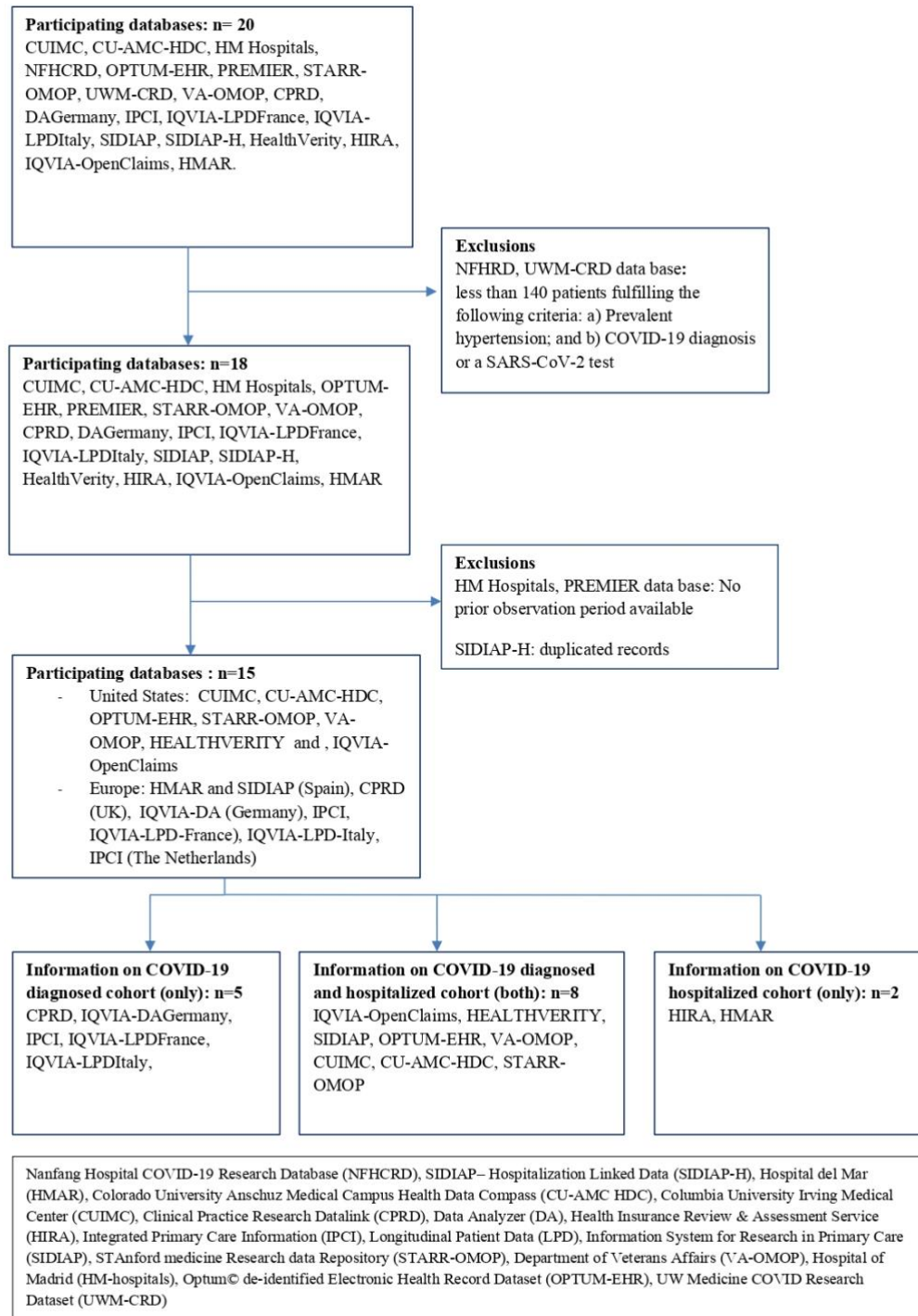


Figure 4. Comorbidities at baseline among patients with a COVID-19 hospitalization with and without hypertension in the CHARYBDIS Network, %. Colour Red=with hypertension, Colour Green=without hypertension.

710x452mm (118 x 118 DPI)

Supporting Figure 1. Flowchart showing the selection of databases included in the analyses



1
2
3
4
5
6 **1 Supporting Table 1. Description of included databases**
7
8
9

10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

Institution Name/ Database	Database Description	Country
Janssen Research & Development The Clinical Practice Research Datalink (CPRD)	The Clinical Practice Research Datalink (CPRD) is a governmental not-for-profit research service jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA) a part of the Department of Health United Kingdom (UK). CPRD consists of data collected from UK primary care for all ages. This includes conditions observations measurements and procedures that the general practitioner is made aware of in addition to any prescriptions as prescribed by the general practitioner. In addition to primary care there are also linked secondary care records for a small number of people. The major data elements contained within this database are outpatient prescriptions given by the general practitioner (coded with Multilex codes) and outpatient clinical referral immunization or test events that the general practitioner knows about (coded in Read or ICD10 or LOINC codes). The database also contains the patients' year of births and any date of deaths.	United Kingdom
IDIAPJGol The Information System for Research in Primary Care (SIDIAP)	The Information System for Research in Primary Care (SIDIAP; www.sidiap.org) is a primary care records database that covers approximately 80% of the population of Catalonia North-East Spain. Healthcare is universal and tax-payer funded in the region and primary care physicians are gatekeepers for all care and responsible for repeat prescriptions.	Spain
Stanford Medicine Research Data Repository (STARR-OMOP)	A clinical data warehouse containing live Epic data from Stanford Health Care the Stanford Children's Hospital	United States

	the University Healthcare Alliance and Packard Children's Health Alliance clinics. Reference: Datta S Posada J Olson G <i>et al.</i> A new paradigm for accelerating clinical data science at Stanford Medicine. <i>arXiv</i> 2020; published online March 17. http://arxiv.org/abs/2003.10534 (accessed Aug 20 2020).	
Columbia University Irving Medical Center (CUIMC)	The clinical data warehouse of New York-Presbyterian Hospital/Columbia University Irving Medical Center New York NY based on its current and previous electronic health record systems with data spanning over 30 years and including over 6 million patients	United States
IQVIA Open Claims	Pre-adjudicated claims covering over 300 Million lives (~80% of the US) collected from office-based physicians and specialists via office management software and clearinghouse switch sources for the purpose of reimbursement.	United States
HIRA Health Insurance Review & Assessment Service	National claim data from a single insurance service from South Korea, It contains the observational medical records (including both inpatient and outpatient) of a patient while they are qualified to get the national medical insurance.	South Korea
HMAR Hospital del mar	Anonymized data from the Electronic Medical Records from Hospital del Mar (Barcelona, Spain). Hospital belonging to the Spanish National Health System (public), attending the Eastern area of Barcelona City. Includes hospital data collected routinely in the clinical practice, both structured and unstructured information, extracted using a free text analysis tool (with natural language processing): Inpatient (hospital) care, Outpatient specialist care, Emergency Room Visits and partial information from other settings like primary care and pharmacy care present in free text notes from EMRs. All subjects with at least one healthcare encounter with the Hospital within approximately last 20 years are included (approximately 0.6 M subjects, with more than	Spain

	5 M hospitalizations/visits). Hospital del Mar data are made available through collaboration with TFS / IOMED.	
OPTUM-EHR Optum® de-identified Electronic Health Record Dataset	Optum ® de-identified Electronic Health Record Dataset is derived from dozens of healthcare provider organizations in the United States (that include more than 700 hospitals and 7,000 Clinics treating more than 103 million patients) receiving care in the United States. The medical record data includes clinical information, inclusive of prescriptions as prescribed and administered, lab results, vital signs, body measurements, diagnoses, procedures, and information derived from clinical Notes using Natural Language Processing (NLP)	United States
IPCI Integrated Primary Care Information	The Integrated Primary Care Information (IPCI) database is collected from EHR records of patients registered with 391 GPs throughout the Netherlands. The database contains records from approximately 2.6 million patients out of a Dutch population of 17M (8.2%) starting in 1996.	The Netherlands
DA Germany IQVIA Disease Analyser Germany	IQVIA DA Germany is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings. Data coverage includes more than 34M distinct person records out of a total population of 80M (42.5%) in the country and collected from 2,734 providers. Dates of service include from 1992 through March 2020	Germany
LPD-Italy IQVIA LPD Italy	LPD Italy is comprised of anonymised patient records collected from software used by GPs during an office visit to document patients' clinical records. Data coverage includes over 2M patient records with at least one visit and 119.5M prescription orders across 900 GP practices. Dates of service include from 2004 through	Italy

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

	present. Observation time is defined by the first and last consultation dates. Drugs are captured as prescription records with product, quantity, dosing directions, strength, indication and date of consultation.	
LPD-France	LPD France is a computerised network of physicians including GPs who contribute to a centralised database of anonymised patient EMR. Currently, >1200 GPs from 400 practices are contributing to the database covering 7.8M patients in France. The database covers a time period from 1994 through the present. Observation time is defined by the first and last consultation dates. Drug information is derived from GP prescriptions. Drugs obtained over the counter by the patient outside the prescription system are not reported	France
HEALTHVERITY	This HealthVerity derived data set contains de-identified patient information with an antibody and/or diagnostic test for COVID-19 linked to all available Medical Claims and Pharmacy Data from select private data providers participating in the HealthVerity marketplace.	United States
University of Colorado Anschutz Medical Campus Health Data Compass (CU-AMC HDC)	Health Data Compass (HDC) is a multi-institutional data warehouse. HDC contains inpatient and outpatient electronic medical data including patient, encounter, diagnosis, procedures, medications, laboratory results from two electronic medical record systems (UCHealth and Children's Hospital of Colorado), state-level all-payers claims data, and the Colorado death registry. Acknowledgement statement: Supported by the Health Data Compass Data Warehouse project (healthdatacompass.org)	
Department of Veterans Affairs VA- OMOP	VA-OMOP data reflects the national Department of Veterans Affairs health care system which is the largest integrated provider of medical and mental health services	United States

in the United States. Care is provided at 170 VA Medical Centers and 1 063 outpatient sites serving more than 9 million enrolled Veterans each year.

Supporting Table 2. Definitions and codes used to identify COVID-19 cases

The below tables summarises the concepts used to identify patients diagnosed with COVID-19 . The full description of the logic used to identify patients diagnosed and hospitalized is provided at <https://atlas.ohdsi.org/#/cohortdefinition/200> and <https://atlas.ohdsi.org/#/cohortdefinition/197> respectively.

COVID-19 condition codes		
Id	Name	Vocabulary
756023	Acute bronchitis due to COVID-19	OMOP Extension
756044	Acute respiratory distress syndrome (ARDS) due to COVID-19	OMOP Extension
756061	Asymptomatic COVID-19	OMOP Extension
756031	Bronchitis due to COVID-19	OMOP Extension
439676	Coronavirus infection	SNOMED
37311061	Disease caused by 2019-nCoV	SNOMED
4100065	Disease due to Coronaviridae	SNOMED
37310284	Encephalopathy caused by 2019 novel coronavirus	SNOMED

37310283	Gastroenteritis caused by 2019 novel coronavirus	SNOMED
4248811	Healthcare associated severe acute respiratory syndrome	SNOMED
756081	Infection of lower respiratory tract due to COVID-19	OMOP Extension
37310286	Infection of upper respiratory tract caused by 2019 novel coronavirus	SNOMED
45763594	Middle East respiratory syndrome	SNOMED
37310287	Myocarditis caused by 2019 novel coronavirus	SNOMED
37310254	Otitis media caused by 2019 novel coronavirus	SNOMED
37310285	Pneumonia caused by 2019 novel coronavirus	SNOMED
37016927	Pneumonia caused by Human coronavirus	SNOMED
40479642	Pneumonia due to Severe acute respiratory syndrome coronavirus	SNOMED
756039	Respiratory infection due to COVID-19	OMOP Extension
320651	Severe acute respiratory syndrome	SNOMED
37396171	Severe acute respiratory syndrome of upper respiratory tract	SNOMED
37311060	Suspected disease caused by 2019-nCoV	SNOMED
COVID-19 specific testing - Positive		
37310282	2019 novel coronavirus detected	SNOMED
COVID-19 specific testing (note these required a corresponding value as concept of: Detected Positive or Present)		

37310255	Detection of 2019 novel coronavirus using polymerase chain reaction technique	SNOMED
700360	Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) amplified probe technique	CPT4
37310258	Measurement of 2019 novel coronavirus antibody	SNOMED
37310257	Measurement of 2019 novel coronavirus antigen	SNOMED
756055	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	OMOP Extension
586310	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Genetic material using Molecular method	OMOP Extension
704991	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Blood	OMOP Extension
756029	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Respiratory specimen	OMOP Extension
586307	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Saliva	OMOP Extension
705107	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Sample from nose	OMOP Extension
586309	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Specified specimen	OMOP Extension
756065	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Unspecified specimen	OMOP Extension
704992	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Culture method	OMOP Extension
705001	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique	OMOP Extension
705000	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Blood	OMOP Extension
756085	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Respiratory specimen	OMOP Extension
586308	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Saliva	OMOP Extension
705106	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Sample from nose	OMOP Extension
756084	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Unspecified specimen	OMOP Extension
704993	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Sequencing	OMOP Extension

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

586516	SARS-CoV-2 (COVID19) [Presence] in Unspecified specimen by Organism specific culture	LOINC
723480	SARS-CoV-2 (COVID19) Ab [Interpretation] in Serum or Plasma	LOINC
586515	SARS-CoV-2 (COVID19) Ab [Presence] in Serum or Plasma by Immunoassay	LOINC
586522	SARS-CoV-2 (COVID19) Ab [Units/volume] in Serum or Plasma by Immunoassay	LOINC
706179	SARS-CoV-2 (COVID19) Ab panel - Serum or Plasma by Immunoassay	LOINC
723477	SARS-CoV-2 (COVID19) Ag [Presence] in Respiratory specimen by Rapid immunoassay	LOINC
706166	SARS-CoV-2 (COVID19) E gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	LOINC
586523	SARS-CoV-2 (COVID19) E gene [Presence] in Respiratory specimen by NAA with probe detection	LOINC
586518	SARS-CoV-2 (COVID19) E gene [Presence] in Serum or Plasma by NAA with probe detection	LOINC
706174	SARS-CoV-2 (COVID19) E gene [Presence] in Unspecified specimen by NAA with probe detection	LOINC
723473	SARS-CoV-2 (COVID19) IgA Ab [Presence] in Serum or Plasma by Immunoassay	LOINC
586521	SARS-CoV-2 (COVID19) IgA Ab [Presence] in Serum Plasma or Blood by Rapid immunoassay	LOINC
723459	SARS-CoV-2 (COVID19) IgA Ab [Units/volume] in Serum or Plasma by Immunoassay	LOINC
757686	SARS-CoV-2 (COVID19) IgA+IgM [Presence] in Serum or Plasma by Immunoassay	LOINC
586527	SARS-CoV-2 (COVID19) IgG Ab [Presence] in DBS by Immunoassay	LOINC
723474	SARS-CoV-2 (COVID19) IgG Ab [Presence] in Serum or Plasma by Immunoassay	LOINC
706181	SARS-CoV-2 (COVID19) IgG Ab [Presence] in Serum Plasma or Blood by Rapid immunoassay	LOINC
706177	SARS-CoV-2 (COVID19) IgG Ab [Units/volume] in Serum or Plasma by Immunoassay	LOINC
706176	SARS-CoV-2 (COVID19) IgG and IgM panel - Serum Plasma or Blood by Rapid immunoassay	LOINC
723479	SARS-CoV-2 (COVID19) IgG+IgM Ab [Presence] in Serum or Plasma by Immunoassay	LOINC

723475	SARS-CoV-2 (COVID19) IgM Ab [Presence] in Serum or Plasma by Immunoassay	LOINC
706180	SARS-CoV-2 (COVID19) IgM Ab [Presence] in Serum Plasma or Blood by Rapid immunoassay	LOINC
706178	SARS-CoV-2 (COVID19) IgM Ab [Units/volume] in Serum or Plasma by Immunoassay	LOINC
706167	SARS-CoV-2 (COVID19) N gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	LOINC
706157	SARS-CoV-2 (COVID19) N gene [Cycle Threshold #] in Unspecified specimen by Nucleic acid amplification using CDC primer-probe set N1	LOINC
706155	SARS-CoV-2 (COVID19) N gene [Cycle Threshold #] in Unspecified specimen by Nucleic acid amplification using CDC primer-probe set N2	LOINC
715272	SARS-CoV-2 (COVID19) N gene [Presence] in Nasopharynx by NAA with probe detection	LOINC
757678	SARS-CoV-2 (COVID19) N gene [Presence] in Nose by NAA with probe detection	LOINC
706161	SARS-CoV-2 (COVID19) N gene [Presence] in Respiratory specimen by NAA with probe detection	LOINC
586524	SARS-CoV-2 (COVID19) N gene [Presence] in Respiratory specimen by Nucleic acid amplification using CDC primer-probe set N1	LOINC
586525	SARS-CoV-2 (COVID19) N gene [Presence] in Respiratory specimen by Nucleic acid amplification using CDC primer-probe set N2	LOINC
586520	SARS-CoV-2 (COVID19) N gene [Presence] in Serum or Plasma by NAA with probe detection	LOINC
706175	SARS-CoV-2 (COVID19) N gene [Presence] in Unspecified specimen by NAA with probe detection	LOINC
706156	SARS-CoV-2 (COVID19) N gene [Presence] in Unspecified specimen by Nucleic acid amplification using CDC primer-probe set N1	LOINC
706154	SARS-CoV-2 (COVID19) N gene [Presence] in Unspecified specimen by Nucleic acid amplification using CDC primer-probe set N2	LOINC
757680	SARS-CoV-2 (COVID19) neutralizing antibody [Presence] in Serum by pVNT	LOINC
757679	SARS-CoV-2 (COVID19) neutralizing antibody [Titer] in Serum by pVNT	LOINC
723469	SARS-CoV-2 (COVID19) ORF1ab region [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	LOINC
706168	SARS-CoV-2 (COVID19) ORF1ab region [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	LOINC
723478	SARS-CoV-2 (COVID19) ORF1ab region [Presence] in Respiratory specimen by NAA with probe detection	LOINC

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

723464	SARS-CoV-2 (COVID19) ORF1ab region [Presence] in Unspecified specimen by NAA with probe detection	LOINC
723471	SARS-CoV-2 (COVID19) RdRp gene [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	LOINC
723470	SARS-CoV-2 (COVID19) RdRp gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	LOINC
706160	SARS-CoV-2 (COVID19) RdRp gene [Presence] in Respiratory specimen by NAA with probe detection	LOINC
706173	SARS-CoV-2 (COVID19) RdRp gene [Presence] in Unspecified specimen by NAA with probe detection	LOINC
586528	SARS-CoV-2 (COVID19) RNA [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	LOINC
586529	SARS-CoV-2 (COVID19) RNA [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	LOINC
715262	SARS-CoV-2 (COVID19) RNA [Log #/volume] (viral load) in Unspecified specimen by NAA with probe detection	LOINC
723476	SARS-CoV-2 (COVID19) RNA [Presence] in Nasopharynx by NAA with non-probe detection	LOINC
586526	SARS-CoV-2 (COVID19) RNA [Presence] in Nasopharynx by NAA with probe detection	LOINC
757677	SARS-CoV-2 (COVID19) RNA [Presence] in Nose by NAA with probe detection	LOINC
706163	SARS-CoV-2 (COVID19) RNA [Presence] in Respiratory specimen by NAA with probe detection	LOINC
715260	SARS-CoV-2 (COVID19) RNA [Presence] in Saliva (oral fluid) by NAA with probe detection	LOINC
715261	SARS-CoV-2 (COVID19) RNA [Presence] in Saliva (oral fluid) by Sequencing	LOINC
723463	SARS-CoV-2 (COVID19) RNA [Presence] in Serum or Plasma by NAA with probe detection	LOINC
706170	SARS-CoV-2 (COVID19) RNA [Presence] in Unspecified specimen by NAA with probe detection	LOINC
706158	SARS-CoV-2 (COVID19) RNA panel - Respiratory specimen by NAA with probe detection	LOINC
706169	SARS-CoV-2 (COVID19) RNA panel - Unspecified specimen by NAA with probe detection	LOINC
723467	SARS-CoV-2 (COVID19) S gene [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	LOINC
723468	SARS-CoV-2 (COVID19) S gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	LOINC

723465	SARS-CoV-2 (COVID19) S gene [Presence] in Respiratory specimen by NAA with probe detection	LOINC
586519	SARS-CoV-2 (COVID19) S gene [Presence] in Serum or Plasma by NAA with probe detection	LOINC
723466	SARS-CoV-2 (COVID19) S gene [Presence] in Unspecified specimen by NAA with probe detection	LOINC
586517	SARS-CoV-2 (COVID19) whole genome [Nucleotide sequence] in Isolate by Sequencing	LOINC
40218805	Testing for SARS-CoV-2 in CDC laboratory	HCPCS
40218804	Testing for SARS-CoV-2 in non-CDC laboratory	HCPCS

Supporting Table 3. Definitions and codes used for hypertension and other comorbidities

Name	Included Codes
Hyperlipidemia	https://atlas.ohdsi.org/#/concept/432867
Chronic kidney disease	https://atlas.ohdsi.org/#/cohortdefinition/312
Cancer	https://atlas.ohdsi.org/#/cohortdefinition/222
Asthma	https://atlas.ohdsi.org/#/cohortdefinition/218
Dementia	https://atlas.ohdsi.org/#/cohortdefinition/226
Total cardiovascular disease	https://atlas.ohdsi.org/#/cohortdefinition/246
Peripheral vascular disease	https://atlas.ohdsi.org/#/concept/321052

Cerebrovascular disease	https://atlas.ohdsi.org/#/concept/381591
Chronic liver disease	https://atlas.ohdsi.org/#/concept/4212540
Chronic obstructive pulmonary disease	https://atlas.ohdsi.org/#/cohortdefinition/219
Heart disease	https://atlas.ohdsi.org/#/cohortdefinition/231
Hypertension	https://atlas.ohdsi.org/#/cohortdefinition/227
Obesity	https://atlas.ohdsi.org/#/cohortdefinition/224
Type 2 Diabetes Mellitus	https://atlas.ohdsi.org/#/cohortdefinition/311

12
13
14

15 **Supporting Table 4. Prevalence of hypertension among COVID-19 patients in the diagnosed and**
16 **hospitalised cohorts in the CHARYBDIS Network.**

	Diagnosed with COVID-19		Hospitalized with COVID-19	
	N of prevalent cases	% (95% CI)	N of prevalent cases	% (95% CI)
IQVIA-OpenClaims-US	1,245,436	48.3 (48.2-48.4)	384,508	76.5 (76.3-76.6)
OPTUM-EHR-US	66,432	37.4 (37.2-37.7)	18,242	64.1 (63.5-64.6)
VA-OMOP-US	34,093	61.4 (61.0-61.8)	8,996	85.9 (85.2-86.6)

HEALTHVERITY-US	25,405	22.3 (22.0-22.5)	4,512	59.5 (58.4-60.6)
SIDIAP-Spain	21,289	17.4 (17.2-17.6)	5,636	31.0 (30.3-31.6)
CUIMC-US	3,672	43.1 (42.1-44.2)	1,708	65.7 (63.9-67.5)
IQVIA-LPD-France	3,260	19.0 (18.4-19.6)	-	-
CU-AMC-HDC-US	2,461	33.9 (32.8-34.9)	904	63.0 (60.5-65.5)
IQVIA-DA-Germany	2,418	30.3 (29.3-31.3)	-	-
HIRA-South Korea	-	-	1943	25.6 (24.6-26.6)
IQVIA-LPD-Italy	1,618	36.1 (34.6-37.5)	-	-
STARR-OMOP-US	1,246	37.4 (35.8-39.1)	342	55.6 (51.7-59.5)
HMAR-Spain	-	-	594	29.5 (27.5-31.5)
CPRD-UK	756	22.4 (21.0-23.8)	-	-
IPCI-The Netherlands	676	22.2 (20.7-23.7)	-	-

17

18

19

20

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	4,5
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	#3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of	6-8

recruitment, exposure, follow-up, and data collection

1			
2			
3	Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.
4			
5			
6	Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed
7			
8			
9			
10	Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
11			
12			
13			
14			
15	Data sources /	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.
16	measurement		
17			
18			
19			
20			
21			
22	Bias	#9	Describe any efforts to address potential sources of bias
23			
24	Study size	#10	Explain how the study size was arrived at
25			
26			
27	Quantitative	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why
28	variables		
29			
30			
31	Statistical	#12a	Describe all statistical methods, including those used to control for confounding
32	methods		
33			
34			
35	9-10		
36			
37	Statistical	#12b	Describe any methods used to examine subgroups and interactions
38	methods		
39			
40			
41	Statistical	#12c	Explain how missing data were addressed
42	methods		
43			
44	Statistical	#12d	If applicable, explain how loss to follow-up was addressed
45	methods		
46			
47			
48	Statistical	#12e	Describe any sensitivity analyses
49	methods		
50			
51			
52	n/a		
53			
54	Results		
55			
56			
57	Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible,
58			
59			
60			

included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.

1			
2			
3			
4			
5	Participants	#13b	Give reasons for non-participation at each stage 10
6			
7	Participants	#13c	Consider use of a flow diagram
8			
9			
10	Supporting figure		
11	1		
12			
13			
14	Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, 10,11 social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.
15			
16			
17			
18			
19	Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest
20			
21			
22			
23	n/a		
24			
25	Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)
26			
27	10		
28			
29			
30	Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.
31			
32			
33			
34			
35	11-16		
36			
37			
38	Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included n/a
39			
40			
41			
42			
43	Main results	#16b	Report category boundaries when continuous variables were categorized Figures 1-4
44			
45			
46			
47	Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
48			
49			
50			
51	n/a		
52			
53	Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses n/a
54			
55			
56			
57	Discussion		
58			
59			
60			

1	Key results	#18	Summarise key results with reference to study objectives	17
2				
3	Limitations	#19	Discuss limitations of the study, taking into account sources of	19
4			potential bias or imprecision. Discuss both direction and magnitude of	
5			any potential bias.	
6				
7				
8	Interpretation	#20	Give a cautious overall interpretation considering objectives,	17-19
9			limitations, multiplicity of analyses, results from similar studies, and	
10			other relevant evidence.	
11				
12				
13	Generalisability	#21	Discuss the generalisability (external validity) of the study results	18-19
14				
15				
16	Other			
17	Information			
18				
19				
20	Funding	#22	Give the source of funding and the role of the funders for the present	22,23
21			study and, if applicable, for the original study on which the present	
22			article is based	
23				
24				
25				
26				

Notes:

- 29 • 13c: Supporting figure 1
- 30
- 31 • 16b: Figures 1-4 The STROBE checklist is distributed under the terms of the Creative Commons
- 32 Attribution License CC-BY. This checklist was completed on 20. September 2021 using
- 33 <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47
- 48
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60