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ORIGINAL ARTICLE

Worldwide impact of COVID-19 on hospital admissions for non-ST-elevation acute coronary syndromes (NSTACS): a systematic review with meta-analysis of 553 038 cases

Francesco Sofi[1], Monica Dinu[1], GianPaolo Reboldi[2,3], Sofia Lotti[1], Luca Genovese[4], Isabella Tritto[5], GianFranco Gensini[4], Charles Michael Gibson[6,†], and Giuseppe Ambrosio[3,5,*,†]

[1]Department of Experimental and Clinical Medicine, University of Florence, Florence 50134, Italy; [2]Department of Medicine, University of Perugia School of Medicine, Perugia 06126, Italy; [3]Center for Clinical and Translational Research—CERICLET, University of Perugia School of Medicine, Perugia 06126, Italy; [4]Department of Cardiology, IRCCS MultiMedica, Milan 20138, Italy; [5]Division of Cardiology, University of Perugia School of Medicine, Perugia 06126, Italy; and [6]Baim Institute for Clinical Research, Harvard Medical School, Boston, MA 02215, USA

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Background How coronavirus disease 2019 (COVID-19) impacted non-ST-segment elevation acute coronary syndromes (NSTACS) is an object of controversial reports.

Aim To systematically review studies reporting NSTACS hospitalizations during the COVID-19 pandemic, and analyse whether differences in COVID-19 epidemiology, methodology of report, or public health-related factors could contribute to discrepant findings.

Methods Comprehensive search (Medline, Embase, Scopus, Web of Science, Cochrane Register), of studies reporting NSTACS hospitalizations during the COVID-19 pandemic compared with a reference period, following Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. Data were independently extracted by multiple investigators and pooled using a random-effects model. Health-related metrics were from publicly available sources, and analysed through multiple meta-regression modelling.

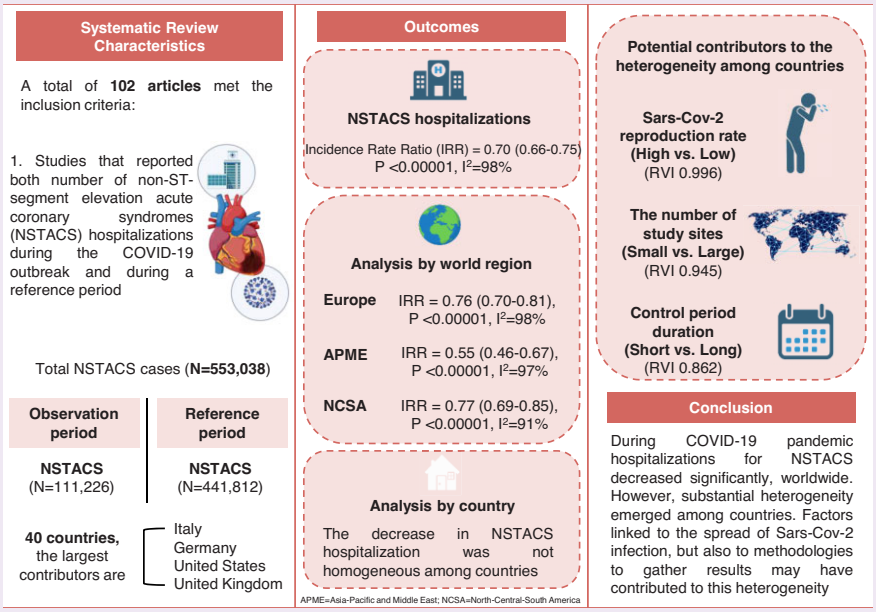
Results We retrieved 102 articles (553 038 NSTACS cases, 40 countries). During peak COVID-19 pandemic, overall incidence rate ratio (IRR) of NSTACS hospitalizations over reference period decreased (0.70, 95% confidence interval (CI) 0.66–0.75; $P < 0.00001$). Significant heterogeneity was detected among studies ($I^2 = 98\%$; $P < 0.00001$). Importantly, wide variations were observed among, and within, countries. No significant differences were observed by study quality, whereas comparing different periods within 2020 resulted in greater decrease (IRR: 0.61; CI: 0.53–0.71) than comparing 2020 vs. previous years (IRR: 0.74; CI 0.69–0.79). Among many variables, major predictors of heterogeneity were severe acute respiratory syndrome coronavirus 2 reproduction rate/country, number of hospitals queried, and reference period length; country stringency index and socio-economical indicators did not contribute significantly.

Conclusions During the COVID-19 pandemic, NSTACS hospitalizations decreased significantly worldwide. However, substantial heterogeneity emerged among countries, and within the same country. Factors linked to public health management, but also to methodologies to collect results may have contributed to this heterogeneity.

Trial registration The protocol was registered in the PROSPERO International Prospective Register of Systematic Reviews (ID: CRD42022308159).

† Both authors share senior authorship.
* Corresponding author. Tel: +39 0755271509, Fax: +39 0755271244, Email: giuseppe.ambrosio@unipg.it

Graphical Abstract



Keywords COVID-19 • Coronavirus • Acute coronary syndromes • Myocardial infarction • NSTEMI • Healthcare organization

Key learning points

a. What is already known:

- Numerous papers have examined the impact of the coronavirus disease 2019 (COVID-19) pandemic on hospital admissions for non-ST-elevation coronary syndromes (NSTACS).
- However, widely disparate findings have been reported, ranging from >60% reduction in NSTACS hospitalizations, to negligible reduction, to even >50 increase.

b. What this study adds:

- To get insight into this huge variability, we systematically meta-analysed all published material on NSTACS hospitalizations, worldwide, encompassing 102 articles (553 038 NSTACS cases, 40 countries).
- Pooling all data, the incidence rate ratio of NSTACS hospitalizations over the reference period significantly decreased (0.70, 95% confidence interval (CI) 0.66–0.75; $P < 0.00001$) during the peak COVID-19 pandemic.
- However, wide variations were observed among, and even within, countries. Predictors of heterogeneity were severe acute respiratory syndrome coronavirus 2 reproduction rate/country, number of hospitals, and reference period length upon which the surveys were based; instead, containment policies and socio-economical indicators did not significantly contribute.

Introduction

Coronavirus disease 2019 (COVID-19) syndrome is dramatically impacting public health in terms of morbidity and mortality caused by respiratory infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus.[1,2] However, of great concern are also the indirect consequences of this pandemic, secondary to huge request and/or re-allocation of health resources. Ambulance services, emergency departments, and intensive care units have been put under pressure to cope with the surge of COVID patients in need of acute care, which at times may have resulted in impaired hospital admission for patients with non-COVID urgent conditions.[3–5] Additionally, underestimating the severity of their condition, many patients with non-COVID emergencies might have been reluctant to seek hospital care out of fear of getting COVID infection, or because of misplaced obedience to stay-at-home orders.[6,7]

This problem has been recognized in regard to hospitalizations for ST-segment elevation myocardial infarction (STEMI), which were expected to increase during COVID pandemic due to possible vascular effects of SARS-CoV-2[8] while instead they significantly decreased.[9,10] In principle, non-ST-segment elevation acute coronary syndromes (NSTACS) could be affected to an even larger extent compared to STEMIs, as patients may suffer less evident symptoms, and diagnosis is at times unclear or elusive.[11–13] Furthermore, unlike STEMIs, in

most places, there is no hub-and-spoke system to expressly dispatch NSTACS patients to a dedicated cardiology department, and therefore transfer and hospital admission of NSTACS patients might be hampered by the concomitant large need of ambulance and intensive care unit beds imposed by COVID patients.

However, evidence about NSTACS hospitalizations during COVID is uncertain, as reports from various countries have yielded widely disparate findings, ranging from >60% reduction in NSTACS hospitalizations,[14–16] to negligible reduction,[17–20] to even >50 increase,[21–24] to quote a few. Aside from differences in COVID-19 epidemiology, variable extent of NSTACS hospitalizations in different regions might have been due to differences in health systems, hospital organization, and socio-economic factors. Differences in methodology to obtain the data might also have contributed.

Understanding how a pandemic impacts NSTACS hospitalizations could translate into better organization of delivery of care for this life-threatening condition, but it might also spur better preparedness for possible future pandemics. Thus, there is a need to accurately estimate the effect of the COVID-19 pandemic on NSTACS hospitalizations across countries, and the potential role not just of differences in SARS-CoV-2 epidemiology but also of other factors.

Accordingly, the purpose of this study was to thoroughly review all available information with respect to the incidence of NSTACS hospitalizations during the COVID-19 pandemic, worldwide, and meta-analyse differences from previous years. Possible factors underlying discrepant results were also evaluated.

Methods

Search strategy

According to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines, all potentially relevant articles were identified searching major electronic databases: Medline, Embase, Scopus, Web of Science, and Cochrane Library, up to 21st April 2022. Comprehensive search criteria were used to identify articles addressing the impact of COVID-19 on admission for NSTACS. The following keywords were used for search: 'covid', 'covid-19', 'sars-cov', 'sars-cov-2', 'coronavirus', AND 'acute coronary*' or 'myocardial infarct*' or 'NSTEMI' or 'non st segment myocardial infarction' or 'non-ST-elevation acute coronary syndromes', or 'NSTACS' (Supplementary material online, *Table S1*). No language restrictions were applied. Online translation tools and language skills of colleagues were used for articles published in languages other than English. Reference lists of the identified studies and previous reviews were also screened. As many earlier reports were not published as full papers, research letters on the topic were also screened. The review was registered on PROSPERO (ID: CRD42022308159).

Data selection

Two authors (M.D., S.L.) independently screened potentially relevant articles for eligibility. The agreement between the two authors in the selection of studies was determined by Cohen's kappa coefficient score. Studies that reported both the number of NSTACS hospitalizations during the COVID-19 outbreak and that during a control (reference) period were considered eligible for inclusion. Eligibility criteria were defined following the PICOS (Population, Intervention, Comparator, Outcome, Study) framework (Supplementary material online, *Table S2*). Decision to include the studies was based on title, abstract (when available), and full-text screening. Studies that specifically included patients who developed NSTACS during hospitalization for COVID-19 infection were excluded.

Data extraction

Two authors (M.D., S.L.) independently extracted data from eligible studies using a standardized data extraction form. Disagreements were resolved by consensus, or by a third reviewer (F.S.) if consensus was not reached. The following data were extracted: first author, year of publication, country of study population, enrollment sites, number of days during study period, number of days during reference period, number of cases during study period, number of cases during reference period, incidence rate (IR) per day during study period and during reference period, and incidence rate ratio (IRR), with their 95% confidence intervals (CIs). When multiple reference periods were presented, we chose the inter-year period (same period but in different years) as reference. If there was a multiple-year comparison (i.e. comparison to historical data from the same months in 2017–19), the entire period was considered as the reference.

Quality assessment

Two authors (S.L., M.D.) independently assessed the methodological quality of the included study using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist for cross-sectional studies.[25] Inconsistencies were discussed and resolved with a third reviewer (F.S.). The STROBE form is a checklist of 22 items considered essential for good study reporting. The items evaluate the title and abstract of the article (Item 1), Introduction (Items 2 and 3), Methods (Items 4–12), Results (Items 13–17), Discussion (Items 18–21), and other information (Item 22, on financing). The results are calculated as the number of the 22 items adequately reported divided by the number of items, expressed as a percentage. Studies with a STROBE score percentage of <55%, 55–65%, and >65% were considered low-, moderate-, and high-quality studies, respectively. Items not applicable for study design were scored as 'not applicable'.

Statistical analysis

Data were analysed using Review Manager (RevMan 5.3 for Macintosh; Copenhagen, Denmark). The results of each study were reported as IR, and IRR of IR during study period over IR during reference period. A random-effects model (DerSimonian and Laird method), which accounts for interstudy variation and provides a more conservative effect than the fixed-effect model, was used. Pooled results were reported as IRRs, and presented with 95% CI with two-sided P values. A P value < 0.05 was considered statistically significant.

Statistical heterogeneity among studies was estimated using the Chi-square Cochran's Q-test with I_2 statistic, which provides an estimate of the amount of variance due to heterogeneity rather than sampling error. Where I_2 exceeded 50%, heterogeneity was considered substantial. Subgroup analyses were performed to explore the source of the heterogeneity, according to the main characteristics of each study [enrolment (hospitals vs. registries); length of observation period (<61 vs. ≥ 61 days, i.e. the median follow-up during observation period); timing of observation period (whole 2020 vs. selected pandemic waves); reference period: inter-year (same period in different years) vs. intra-year (different period of the same year, or different periods of different years); and study quality (high, medium, low)]. The possibility of publication bias was explored by visual inspection of funnel plot.

Meta-regression analysis

To further explore heterogeneity and identify potential effect modifiers at study and country levels, we used random-effects meta-regression.[26,27] From the 'Our World in Data' Coronavirus database[28] as on the date of completion of the study, for each country we extracted the following variables: total SARS-CoV-2 cases/million, SARS-CoV-2 reproduction rate, total COVID-19 deaths/million, stringency index, population density, cardiovascular death rate, hospital beds/thousand, number of physicians/thousand, gross domestic product per capita, human development index, World Bank Region assignment, and WHO Region.[29] In addition, we also tested the impact of reference period (same vs. previous year), reference period length, study setting (registry vs. survey), quality of study, and number of hospital sites from which data were gathered.

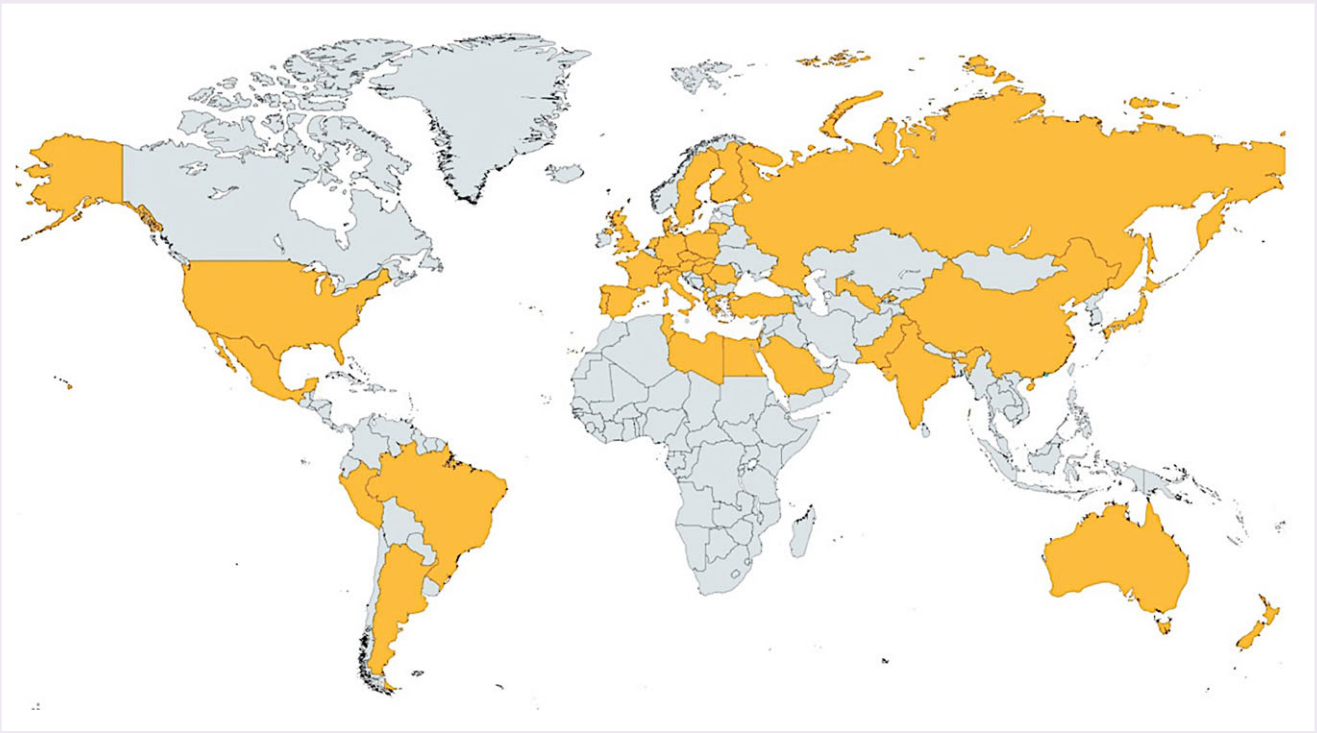


Figure 1 World map highlighting (in orange) all 40 countries for which NSTACS admission data during the COVID-19 pandemic peak were reported and utilized for this meta-analysis.

We built a multiple meta-regression model using multimodel inference.[30] With this method all possible predictor combinations are modelled, and although this approach should be regarded as exploratory, it can be used when there is little or no prior knowledge on how predictors are related to the effect size. The goal of the method is to distinguish 'true' from 'false' moderators using their relative variable importance (RVI). We first computed the RVI using the Akaike weight of each model, and then used the RVI as the selection criteria with cutoff values greater than 0.5 or 0.8 for considering a variable important for inference.[30]

Results

Literature search and study characteristics

The selection process according to PRISMA guidelines is shown in Supplementary material online, *Figure S1*. Database and other searches yielded 5750 articles. After review of title and abstract, and removal of duplicates, 173 articles were selected for analysis. Of these, 71 were excluded based on full-text evaluation. At the end of the process, 102 articles met all inclusion criteria, encompassing a total of 553 038 NSTACS cases from 40 countries (*Figure 1*), and were included in the analysis. The Cohen's kappa coefficient was 0.893, suggesting an excellent agreement between the two authors in the selection of studies.

Table 1 summarizes the characteristics of the studies included in this systematic review. A total of 15 studies were conducted in Italy, 10 in Germany, and 9 in the USA; other countries contributed fewer reports. Another three studies were multinational. In most cases (83 articles), data were collected through 'ad hoc' surveys of selected hospitals, whereas 19 studies reported data obtained from already ongoing registries or health-insurance funds. All studies chose the year 2020 as observation timing. Median length of observation period was 61 days (range 7–366 days). Three different selection methods were found for the reference period: (a) same period of year 2019; (b) a period immediately preceding observation period; and (c) average of same period of previous years. Median length of reference period was 71 days (range 7–1176 days).

Overall analysis includes a total of 111 226 cases of NSTACS during observation period, and 441 812 cases during reference period. Based on STROBE checklist, quality was high in 73 studies (71.6%), moderate in 13 studies (12.7%), and low in 18 studies (15.6%) (Supplementary material online, *Table S3*).

Meta-analytic results

Figure 2 shows the Forest plot of studies reporting hospitalizations for NSTACS during the COVID-19 peak compared to the reference period in all studies, by World region and by country. IRR under a random-effect model for all studies showed a significant reduction in the number of hospitalizations for NSTACS (0.70, 95% CI 0.66–0.75; $P < 0.00001$) during COVID-19 epidemic compared with the reference period. Of note, a high degree of heterogeneity was found ($I^2 = 98\%$; $P < 0.00001$). Analysis by World region showed differences among geographic areas. While 24% reduction in NSTACS hospitalizations was reported for Europe (IRR 0.76, 95% CI 0.70–0.81), the reduction for North-Central-South America region was 33% (0.77, 95% CI 0.69–0.85), and for Asia-Pacific–Middle East it was 45% (0.55, 95% CI 0.46–0.67) (all $P < 0.00001$).

However, when the analysis delved into country-specific data, further heterogeneity emerged, as the decrease in NSTACS hospitalization was not homogeneous among countries (*Figure 3*). While many countries reported ~30% decrease in NSTACS hospitalizations, and other showed 50% or more decrease, reports from other countries indicated only <5% decrease (Finland, Hong Kong, and Hungary), or even an increase in NSTACS hospitalizations (Israel, Denmark, and

Table 1 Characteristics of studies evaluating the impact of the COVID-19 pandemic on hospital admissions for NSTEACS included in the systematic review

Author, year	Country	Enrolment sites	*N* days (study period)	*N* days (control period)	*N* cases, study period	*N* cases, control period	IR study period	IR control period	IRR (95% CI)	Quality*
Adnan *et al.*, 2021	Pakistan (Karachi)	1 hospital	153 (1st March–31st July 2020)	153 (1st March–31st July 2019)	129	409	0.84	2.67	0.31 (0.25–0.38)	++
Aktaa *et al.*, 2022	UK	186 NHS hospitals	65 (23rd March–27th May 2020)	1176 (1st January, 2017–22nd March 2020)	6679	145 430	119.27	123.66	0.96 (0.94–0.98)	++
Aldujeli *et al.*, 2020	Lithuania (Kaunas)	1 hospital	37 (1st March–20th April 2020)	37 (1st March–20th April 2019)	30	62	0.81	1.68	0.48 (0.31–0.74)	++
Alhejily *et al.*, 2021	Saudi Arabia	1 hospital	366 (1st January–31st December 2020)	365 (1st January–31st December 2019)	28	16	0.08	0.04	1.75 (0.94–3.23)	++
Arai *et al.*, 2021	Japan (Tokyo)	1 hospital	243 (30th January–30th September 2020)	484 (30th January–30th September 2017 and 2019)	13	54	0.05	0.11	0.45 (0.25–0.82)	++
Araiza-Garaygordobil *et al.*, 2021	Spain, Italy, Austria, Poland, Saudi Arabia, Egypt, Romania, Argentina, France, Greece, México, Perú, Turkey, Serbia, Portugal, Libya, Uzbekistan	29 hospitals	23 (12th March–15th April 2020)	120 (1st December 2018–1st April 2019)	712	5215	30.96	43.46	0.71 (0.66–0.77)	++
Arias-Mendoza *et al.*, 2021	México	1 hospital	69 (23rd March–31st May 2020)	69 (23rd March–31st May 2019)	36	53	0.52	0.77	0.68 (0.45–1.04)	-
Asher *et al.*, 2021	Israel	13 hospitals	56 (11th March–6th May 2020)	56 (11th March–6th May 2018)	349	275	6.23	4.91	1.27 (1.08–1.49)	-
Barbero *et al.*, 2020	Italy (Northern Italy)	15 hospitals	41 (20th February–31st March 2020)	40 (20th February–31st March 2019)	173	305	4.33	7.82	0.55 (0.46–0.66)	++
Behrendt *et al.*, 2021	Germany	1 National registry (BARMER)	122 (1st March–30th June 2020)	366 (1st March–30th June 2017–2019)	1351	4794 (3 years)	11.07	13.10	0.85 (0.80–0.90)	++

Table I **Continued**

Author, year	Country	Enrolment sites	*N* days (study period)	*N* days (control period)	*N* cases, study period	*N* cases, control period	IR study period	IR control period	IRR (95% CI)	Quality*
Boukhris *et al.*, 2021	Russia, Brazil, Saudi Arabia, Tunisia	8 hospitals	121 (1st January–30th April 2020)	120 (1st January–30th April 2019)	1041	1087	8.60	9.06	0.95 (0.87–1.03)	-
Braiteh *et al.*, 2020	USA (Upstate New York)	4 hospitals	61 (1st March–30th April 2020)	61 (1st March–30th April 2019)	44	85	0.72	1.39	0.52 (0.36–0.75)	++
Budrys *et al.*, 2021	Lithuania (Vilnius)	1 hospital	122 (1st March–30th June 2020)	122 (1st March–30th June 2019)	132	155	1.08	1.27	0.85 (0.67–1.07)	++
Bugger *et al.*, 2020	Austria	11 hospitals	42 (16th March–26th April 2020)	168 (16th March–26th April 2016–19)	91	498 (4 years)	2.17	2.96	0.73 (0.58–0.91)	++
Caamaño *et al.*, 2020	Spain (La Gomera Canary Island)	1 hospital	35 (4th March–19th April 2020)	47 (17th January–3rd March 2020)	19	29	0.54	0.62	0.87 (0.49–1.55)	-
Campanile *et al.*, 2021	Italy	6 hospitals	30 (10th March–9th April 2020)	29 (8th February–9th March 2020)	40	102	1.33	3.52	0.38 (0.26–0.55)	++
Campo *et al.*, 2021	Italy (Emilia-Romagna)	1 Regional registry	81 (22nd February–13th May 2020)	52 (1st January–21st February 2020)	780	814	9.63	15.65	0.62 (0.56–0.68)	++
Chan et al., 2020	New Zealand	National registry (ANZACSQI)	34 (23rd March–26th April 2020)	170 (23rd March–26th April 2015–2019)	361	2740 (5 years)	10.62	16.12	0.66 (0.59–0.74)	++
Choudhary et al., 2020	India (Western India)	4 hospitals	30 (25th March–24th April 2020)	58 (25th January–24th March 2020)	36	840	1.20	14.48	0.08 (0.06–0.11)	++
Choudhary et al., 2021	India	4 hospitals	130 (25th March–2nd June 2020)	69 (15th January–24th March 2020)	37	504	0.28	7.30	0.04 (0.03–0.06)	-
De Rosa *et al.*, 2020	Italy (Piedmont, Lombardy, Latium, Calabria, Liguria, Tuscany, Veneto, Campania, Emilia-Romagna, Sardinia, Umbria, Apulia, Friuli, Trentine, Sicily, Basilicata)	54 hospitals	7 (12th–19th March 2020)	7 (12th–19th March 2019)	122	350	17.4	50.0	0.35 (0.28–0.43)	++

Table 1 Continued

Author, year	Country	Enrolment sites	*N* days (study period)	*N* days (control period)	*N* cases, study period	*N* cases, control period	IR study period	IR control period	IRR (95% CI)	Quality*
Eckner *et al.*, 2021	Germany (Hamburg, Nuremberg)	2 hospitals	124 (1st January–3rd May 2020)	125 (1st January–5th May 2019)	336	302	2.71	2.42	1.12 (0.96–1.31)	++
Erol *et al.*, 2020	Turkey	15 hospitals	15 (17th April–2nd May 2020)	15 (1st November–15th November 2019)	506	1161	33.7	77.4	0.44 (0.40–0.49)	++
Ferreira *et al.*, 2020	Australia	1 hospital	69 (23rd March–31st May 2020)	138 (23rd March–31st May 2018–2019)	129	407 (2 years)	1.87	2.95	0.64 (0.53–0.78)	++
Fileti *et al.*, 2020	Italy (Emilia-Romagna)	2 hospitals	32 (10th March–10th April 2020)	32 (10th March–10th April 2019)	38	58	1.19	1.81	0.66 (0.44–0.99)	++
Fox *et al.*, 2022	USA (St. Louis)	12 hospitals	186 (21st March–21st September 2020)	809 (1st January, 2018–20th March 2020)	622	3682	3.34	4.55	0.73 (0.67–0.79)	++
Gaspardone *et al.*, 2021	Italy (Rome)	9 hospitals	19 (10th–29th March 2020)	18 (19th February–9th March 2020)	70	99	3.68	5.50	0.67 (0.49–0.91)	++
Gitt *et al.*, 2020	Germany (Ludwigshafen)	1 hospital	61 (1st March–30th April 2020)	61 (1st March–30th April 2019)	50	95	0.82	1.56	0.53 (0.38–0.75)	-
Gluckman *et al.*, 2020	USA (Alaska, Washington, Montana, Oregon, California, Texas)	49 hospitals	84 (23rd February–16th May 2020)	420 (30th December 2018–22nd February 2020)	1271	9009	15.1	21.5	0.71 (0.67–0.75)	++
Grave *et al.*, 2021	France	1 National registry (SNDS)	119 (2nd February–31st May 2020)	354 (2nd February–31st May 2017–2019)	46 314	145 189 (3 years)	389.19	410.14	0.95 (0.94–0.96)	++
Hauguel-Moreau *et al.*, 2020	France (Boulogne)	1 hospital	69 (17th February–26th April 2020)	136 (17th February–26th April 2018–19)	21	44 (2 years)	0.30	0.32	0.94 (0.56–1.58)	-
Hawranek *et al.*, 2021	Poland	1 National registry (PL-ACS)	92 (1st March–31st May 2020)	92 (1st March–31st May 2019)	2150	5017	23.37	54.53	0.43 (0.41–0.45)	+

Table I Continued

Author, year	Country	Enrolment sites	*N* days (study period)	*N* days (control period)	*N* cases, study period	*N* cases, control period	IR study period	IR control period	IRR (95% CI)	Quality*
He *et al.*, 2022	China	1 City registry (Beijing Municipal Health Commission Information Center database)	213 (1st December 2019–30th June, 2020)	212 (1st December 2018–30th June, 2019)	1991	3373	9.35	15.91	0.59 (0.56–0.62)	++
Hussain *et al.*, 2021	UK	1 hospital	61 (1st April–31st May 2020)	61 (1st April–31st May 2019)	59	56	0.97	0.92	1.05 (0.73–1.51)	-
Huynh *et al.*, 2021	Sweden (Jönköping County)	3 hospitals	153 (1st March–31st July 2020)	459 (1st March–31st July 2017–2019)	162	542 (3 years)	1.06	1.18	0.90 (0.76–1.07)	++
Kapelios *et al.*, 2020	Greece (Athens)	1 hospital	151 (1st February–30th June 2020)	215 (1st July, 2019–31st January 2020)	27	69	0.18	0.32	0.56 (0.36–0.87)	+
Katsouras *et al.*, 2021	Greece (Athens, Thessaloniki, Ioannina)	3 hospitals	42 (2nd March–12th April 2020)	42 (2nd March–12th April 2019)	80	110	1.90	2.62	0.73 (0.55–0.97)	++
Kessler *et al.*, 2020	Germany	15 hospitals	61 (1st March–30th April 2020)	61 (1st March–30th April 2019)	1100	1482	18.0	24.3	0.74 (0.68–0.80)	-
Khan *et al.*, 2020	Pakistan (Rawalpindi)	1 hospital	37 (1st April–7th May 2020)	37 (1st April–7th May 2019)	207	748	5.59	20.22	0.28 (0.24–0.33)	+
Kiblboeck *et al.*, 2020	Austria	19 hospitals	14 (16th March–29th March 2020)	14 (2nd March–15th March 2020)	146	259	10.4	18.5	0.56 (0.46–0.69)	-
Kudo *et al.*, 2021	Japan (Tokai)	11 hospitals	61 (1st April–31st May 2020)	61 (1st April–31st May 2019)	47	47	0.77	0.77	1.00 (0.67–1.50)	++
Kundi *et al.*, 2021	Turkey	1 National registry	61 (1st March–30th April 2020)	122 (1st March–30th April 2018–2019)	5087	18 862 (2 years)	83.39	154.61	0.54 (0.52–0.56)	+
Kutlay *et al.*, 2020	Turkey	1 hospital	61 (1st March–30th April 2020)	61 (1st March–30th April 2019)	52	53	0.85	0.87	0.98 (0.67–1.44)	-
Lauridsen *et al.*, 2020	Denmark	1 National registry (Danish Civil Population Registry)	32 (12th March–13th May 2020)	160 (12th March–13th May 2015–2019)	9	59 (4 years)	0.28	0.37	0.76 (0.38–1.53)	++

Table 1 Continued

Author, year	Country	Enrolment sites	*N* days (study period)	*N* days (control period)	*N* cases, study period	*N* cases, control period	IR study period	IR control period	IRR (95% CI)	Quality*
Lavie *et al.*, 2022	Israel	1 National registry (Clalit Health Services)	41 (2nd March–12th April 2020)	123 (2nd March–12th April 2017–2019)	735	2640 (3 years)	17.93	21.46	0.84 (0.77–0.91)	++
Legutko *et al.*, 2020	Poland	11 hospitals	31 (15th March–14th April 2020)	74 (1st January–14th March 2020)	202	292	6.52	3.95	1.65 (1.38–1.97)	+
Liu *et al.*, 2020	China (Beijing)	1 hospital	60 (1st February–31st March 2020)	59 (1st February–31st March 2019)	115	145	1.92	2.46	0.78 (0.61–1.00)	++
L'Angiocola *et al.*, 2021	Italy (Gorizia)	1 hospital	60 (1st February–31st March 2020)	59 (1st February–31st March 2019)	22	34	0.37	0.58	0.64 (0.37–1.09)	+
Ma *et al.*, 2021	China (Shunde, Haikou)	2 hospitals	91 (23rd January–23rd April 2020)	90 (23rd January–23rd April 2019)	84	96	0.92	1.07	0.86 (0.64–1.15)	++
Mafham *et al.*, 2020	UK	147 NHS hospitals	7 (23rd March–30th March 2020)	7 (2019 weekly average)	733	1267 (weekly average)	104.7	181.0	0.58 (0.53–0.64)	++
Makaris *et al.*, 2021	Greece (Messinia)	1 hospital	54 (10th March–3rd May 2020)	108 (10th March–3rd May 2018–2019)	25	80 (2 years)	0.46	0.74	0.62 (0.40–0.97)	++
Matsushita *et al.*, 2020	France (Strasbourg)	1 hospital	51 (1st March–20th April 2020)	51 (1st March–20th April 2019)	53	119	1.04	2.33	0.45 (0.33–0.62)	++
Meenakshisundaram *et al.*, 2020	India (Madurai, Trichy, Erode, Salem)	12 hospitals	30 (1st–30th April 2020)	30 (1st–30th April 2019)	183	547	6.10	18.23	0.33 (0.28–0.39)	++
Mefford *et al.*, 2021	USA (Southern California)	KPSC registry	213 (1st January–31st July 2020)	212 (1st January–31st July 2019)	2625	2902	12.32	13.69	0.90 (0.85–0.95)	++
Mesnier *et al.*, 2020	France	21 hospitals	28 (17th March–12th April 2020)	28 (17th February–16th March 2020)	355	229	12.7	8.2	1.55 (1.31–1.83)	++
Metzler *et al.*, 2020	Austria	1 National registry	7 (23rd March–29th March 2020)	7 (2nd March–8th March 2020)	67	132	9.57	18.9	0.51 (0.38–0.68)	-

Table I Continued

Author, year	Country	Enrolment sites	*N* days (study period)	*N* days (control period)	*N* cases, study period	*N* cases, control period	IR study period	IR control period	IRR (95% CI)	Quality*
Mitra *et al.*, 2020	Australia	1 hospital	28 (26th March–23rd April 2020)	28 (26th March–23rd April 2019)	14	17	0.50	0.61	0.82 (0.40–1.66)	++
Mohammad *et al.*, 2020	Sweden	29 hospitals	68 (1st March–7th May 2020)	340 (1st March–7th May 2015–2019)	1544	9399 (5 years)	22.7	27.6	0.82 (0.73–0.92)	++
Montagnon *et al.*, 2020	France (Toulon)	1 hospital	14 (23rd March–5th April 2020)	14 (23rd March–5th April 2029)	4	9	0.29	0.64	0.45 (0.14–1.46)	++
Mousavi *et al.*, 2021	Austria	1 hospital	105 (15 lockdown weeks in 2020)	252 (36 weeks without lockdown in 2020)	28	47	0.27	0.19	1.42 (0.89–2.27)	+
Nef *et al.*, 2021	Germany	22 public health authorities	34 (23rd March–26th April 2020)	34 (23rd March–26th April 2019)	560	750	16.47	22.06	0.75 (0.67–0.84)	++
Noorali *et al.*, 2021	Pakistan (Aga Khan)	1 hospital	122 (1st March–30th June 2020)	122 (1st March–30th June 2019)	176	269	1.44	2.20	0.65 (0.54–0.79)	++
Oikonomou *et al.*, 2020	Greece	3 hospitals	35 (9th March–12th April 2020)	25 (9th March–2nd April 2019)	39	96	1.11	3.84	0.29 (0.20–0.42)	++
Olié *et al.*, 2021	France	1 National register (OSCUR)	77 (16nd March–31st May 2020)	42 (3nd February–15th March 2020)	3147	2001	40.87	47.64	0.86 (0.81–0.91)	++
Østergaard *et al.*, 2020	Denmark	1 National registry	127 (1st January–6th May 2020)	381 (1st January–7th May 2017–19)	1039	3027 (3 years)	8.25	8.01	1.03 (0.96–1.11)	++
Pacheco *et al.*, 2021	Portugal	1 hospital	153 (1st March–31st July 2020)	153 (1st March–31st July 2019)	60	72	0.39	0.47	0.83 (0.59–1.17)	+
Papafaklis *et al.*, 2020	Greece	1 National registry	42 (2nd March–12th April 2020)	42 (2nd March–12th April 2019)	352	479	8.38	11.4	0.74 (0.64–0.85)	++
Petrović *et al.*, 2021	Serbia (Vojvodina)	1 hospital	51 (16th March–6th May 2020)	51 (16th March–6th May 2019)	31	56	0.61	1.10	0.55 (0.35–0.85)	++

Table 1 Continued

Author, year	Country	Enrolment sites	*N* days (study period)	*N* days (control period)	*N* cases, study period	*N* cases, control period	IR study period	IR control period	IRR (95% CI)	Quality*
Piccolo *et al.*, 2020	Italy (Campania)	20 hospitals	28 (27th February–26th March 2020)	28 (30th January–26th February 2020)	244	360	8.71	12.9	0.68 (0.58–0.80)	+
Pines *et al.*, 2021	USA	108 hospitals	238 (1st January–25th August 2020)	237 (1st January–25th August 2019)	8424	9278	35.39	39.15	0.90 (0.87–0.93)	++
Primessnig *et al.*, 2021	Germany (Berlin)	1 hospital	121 (1st January–30th April 2020)	120 (1st January–30th April 2019)	25	61	0.21	0.51	0.41 (0.26–0.65)	++
Rashidn Hons *et al.*, 2020	UK	2 National registries (Myocardial Ischaemia National Audit Project, British Cardiovascular Intervention Society)	104 (1st February–14th May 2020)	103 (1st February–14th May 2019)	145	193	1.39	1.87	0.74 (0.60–0.92)	++
Rattka *et al.*, 2020	Germany (Ulm)	1 hospital	31 (21st March–20th April 2020)	93 (21st March–20th April 2017–19)	16	104 (3 years)	0.52	1.12	0.46 (0.27–0.78)	++
Rognoni *et al.*, 2021	Italy	9 hospitals	38 (4th May–12th July 2020)	38 (4th May–12th July 2019)	NA	NA	-	-	1.25 (1.08–1.46)	++
Rossi *et al.*, 2021	Italy (Brescia)	1 hospital	83 (9th March–31st May 2020)	68 (1st January–8th March 2020)	28	36	0.34	0.53	0.64 (0.39–1.05)	++
Ruparelia *et al.*, 2020	UK (London)	2 hospitals	103 (1st January–12th April 2020)	102 (1st January–12th April 2019)	97	135	0.94	1.32	0.71 (0.55–0.92)	++
Schmitz *et al.*, 2021	Germany (Augsburg)	1 regional registry	66 (16th March–21st May 2020)	33 (10th February–15th March 2020)	66	51	1.00	1.55	0.65 (0.45–0.94)	++
Schwarz *et al.*, 2020	Germany (Saarland)	1 hospital	42 (1st March–18th April 2020)	42 (3rd March–20th April 2019)	29	35	0.69	0.83	0.83 (0.51–1.36)	++
Secco *et al.*, 2020	Italy (Northern and Central Italy)	3 hospitals	31 (1st–31st March 2020)	31 (1st–31st March 2019)	33	93	1.06	3.0	0.35 (0.24–0.52)	++

Table I Continued

Author, year	Country	Enrolment sites	*N* days (study period)	*N* days (control period)	*N* cases, study period	*N* cases, control period	IR study period	IR control period	IRR (95% CI)	Quality*
Seiffert *et al.*, 2020	Germany	Health insurance fund	152 (1st February–31th May 2020)	151 (1st February–31th May 2019)	6518	7682	42.9	50.9	0.84 (0.81–0.87)	++
Showkathali *et al.*, 2020	India	1 hospital	67 (25th March–31st May 2020)	134 (25th March–31st May 2018–2019)	39	60 (2 years)	0.58	0.45	1.29 (0.86–0.93)	+
Simoni *et al.*, 2021	Albania (Tirana)	1 hospital	42 (19th March–30th April 2020)	42 (19th March–30th April 2019)	165	333	3.93	7.93	0.50 (0.41–0.60)	++
Skodaa *et al.*, 2020	Hungary	1 hospital	56 (26th February–22nd April 2020)	110 (26th February–22nd April 2018–2019)	54	111 (2 years)	0.96	1.01	0.95 (0.69–1.32)	++
Sokolski *et al.*, 2020	Poland, The Netherlands, Sweden, Portugal, Switzerland, Italy, Hungary, UK, Germany, France, Spain, USA	15 hospitals	31 (1st March–30th April 2020)^	31 (1st March–30th April 2019)^	406	720	13.1	23.23	0.56 (0.50–0.63)	++
Solomon *et al.*, 2020	USA (Northern California)	21 hospitals	105 (1st January–14th April 2020)	105 (1st January–15th April 2019)	1198	1322	11.4	12.6	0.91 (0.84–0.98)	++
Sulzgruber *et al.*, 2020	Austria (Vienna)	1 City registry	29 (13th March–10th April 2020)	29 (13th March–10th April 2019)	33	46	1.14	1.59	0.72 (0.46–1.13)	++
Sutherland *et al.*, 2022	Australia (Melbourne)	1 hospital	61 (1st March–30th April 2020)	61 (1st March–30th April 2019)	61	105	1.00	1.72	0.58 (0.42–0.80)	++
Tam *et al.*, 2020	Hong Kong (Hong Kong)	1 hospital	66 (25th January–31st March 2020)	85 (1st November 2019–24th January 2020)	37	49	0.56	0.58	0.97 (0.63–1.49)	++
Tan *et al.*, 2020	USA (Los Angeles)	1 hospital	28 (16th March–12th April 2020)	84 (23rd December, 2019–15th March 2020)	26	106	0.93	1.26	0.74 (0.48–1.14)	+
Toniolo *et al.*, 2020	Italy (Udine)	1 hospital	31 (1st March–31st March 2020)	31 (1st March–31st March 2019)	15	44	0.48	1.42	0.34 (0.19–0.61)	-
Toušek *et al.*, 2020	Czech Republic (Prague)	1 hospital	120 (1st February–30th May 2020)	488 (1st October, 2018–31st January 2020)	80	359	0.67	0.74	0.91 (0.71–1.16)	++

Table 1 Continued

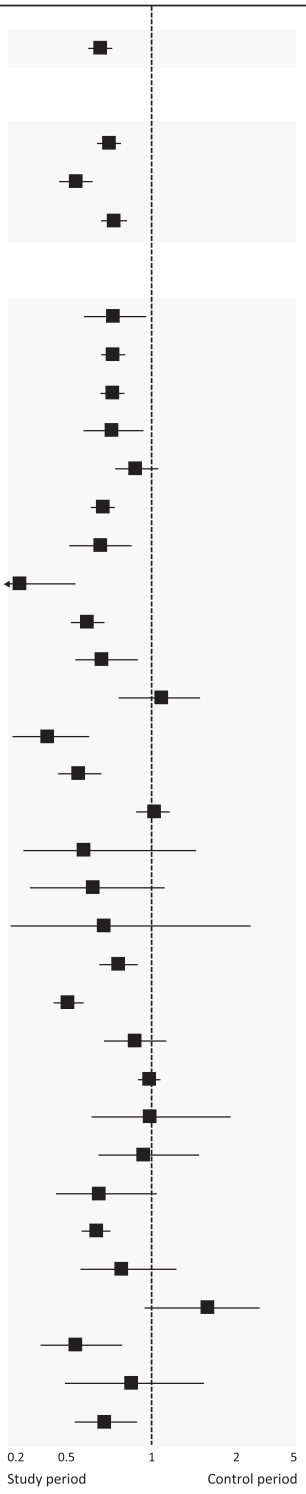
Author, year	Country	Enrolment sites	*N* days (study period)	*N* days (control period)	*N* cases, study period	*N* cases, control period	IR study period	IR control period	IRR (95% CI)	Quality*
Trabattoni *et al.*, 2021	Italy (Milan)	1 hospital	366 (1st January–31st December 2020)	365 (1st January–31st December 2019)	271	162	0.74	0.44	1.68 (1.38–2.04)	-
Tsigkas *et al.*, 2021	Greece (Southern Greece)	3 hospitals	55 (10th March–4th May 2020)	110 (10th March–4th May 2018–2019)	75	221 (2 years)	1.36	2.01	0.68 (0.52–0.88)	++
Uimonen *et al.*, 2022	Finland	3 hospitals	92 (1st March–31st May 2020)	276 (1st March–31st May 2017–2019)	NA	NA	-	-	0.98 (0.94–1.02)	++
Ullah *et al.*, 2021	UK	1 hospital	68 (23rd March–30th May 2020)	71 (23rd March–2nd June 2019)	118	186	1.74	2.62	0.66 (0.52–0.83)	+
Versaci *et al.*, 2020	Italy (Latina)	1 hospital	19 (1st March–19th March 2020)	19 (1st March–19th March 2019)	13	51	0.68	2.68	0.25 (0.14–0.46)	-
Wagle *et al.*, 2022	USA	1 hospital	184 (1st March–31st August 2020)	184 (1st March–31st August 2019)	103	107	0.56	0.58	0.97 (0.74–1.27)	-
Walker *et al.*, 2020	USA (Rochester, Jacksonville, Scottdale)	19 hospitals	35 (17th March–21st April 2020)	35 (17th March–21st April 2019)	63	152	1.80	4.34	0.41 (0.31–0.55)	++
Wiessman *et al.*, 2021	Israel	2 hospitals	61 (1st March–30th April 2020)	61 (1st March–30th April 2019)	85	69	1.39	1.13	1.23 (0.90–1.69)	+
Wu *et al.*, 2021	UK	99 NHS hospitals	61 (23rd March–22nd May 2020)	447 (1st January, 2019–22nd March 2020)	2534	30 909	41.54	69.15	0.60 (0.58–0.62)	++
Zachariah *et al.*, 2021	India	187 hospitals	92 (15th March–15th June 2020)	92 (15th March–15th June 2019)	5285	9363	57.45	101.77	0.56 (0.54–0.58)	++
Zorzi *et al.*, 2020	Italy (Padua)	1 hospital	92 (1st March–31st May 2020)	92 (1st March–31st May 2019)	70	64	0.76	0.70	1.09 (0.78–1.53)	++

IR = incidence rate; IRR = incidence rate ratio; NSTEMI = non-ST-segment elevation myocardial infarction.

[a]Quality of included studies expressed as % of STROBE checklist criteria met: >65% = ++; 55–65% = +; <55% = −.

[b]The period differed across participating European countries depending on the 'peak month' of SARS-CoV-2 infection at a particular centre (decision which period to select was left at the discretion of the investigator) but was limited to a period between 1 March 2020 and 30 April 2020.

	n° of studies	n cases, study period	n cases, control period	Incidence Rate Ratio (Random, 95% CI)	Incidence Rate Ratio (95% CI)	P-value	I^2, %	P-het
All studies	102	111,226	441,812		0.70 [0.66, 0.75]	<0.00001	98%	<0.00001
World region								
Europe	67	83,163	380,527		0.76 [0.70, 0.81]	<0.00001	98%	<0.00001
APME	22	10,141	22,773		0.55 [0.46, 0.67]	<0.00001	97%	<0.00001
NCSA	10	14,412	26,696		0.77 [0.69, 0.85]	<0.00001	91%	<0.00001
Country								
Italy	15	1,919	2,572		0.78 [0.63, 0.97]	0.02	91%	<0.00001
Germany	10	10,051	15,356		0.78 [0.71, 0.85]	<0.00001	82%	<0.00001
United States	9	14,376	26,643		0.77 [0.70, 0.86]	<0.00001	92%	<0.00001
United Kingdom	7	10,365	178,176		0.73 [0.57, 0.94]	0.01	99%	<0.00001
France	6	49,894	147,591		0.92 [0.79, 1.08]	0.30	93%	<0.00001
Greece	6	598	1,055		0.72 [0.65, 0.80]	<0.00001	0%	0.68
Austria	5	365	982		0.70 [0.53, 0.92]	0.01	76%	0.002
India	5	5,580	11,314		0.24 [0.10, 0.56]	0.001	99%	<0.00001
Australia	3	204	529		0.63 [0.54, 0.74]	<0.00001	0%	0.66
China	3	2,190	3,614		0.71 [0.55, 0.92]	0.01	81%	0.001
Israel	3	1,169	2,984		1.08 [0.78, 1.49]	0.64	92%	<0.00001
Pakistan	3	512	1,426		0.38 [0.23, 0.64]	0.0003	96%	<0.00001
Turkey	3	5,645	20,076		0.56 [0.45, 0.70]	<0.00001	91%	<0.00001
Denmark	2	1,048	3,086		1.03 [0.96, 1.10]	0.46	0%	0.40
Japan	2	60	101		0.69 [0.32, 1.51]	0.36	78%	0.03
Lithuania	2	162	217		0.66 [0.38, 1.15]	0.14	81%	0.02
Poland	2	2,352	5,309		0.84 [0.22, 3.14]	0.80	100%	<0.00001
Sweden	2	1,706	9,941		0.83 [0.79, 0.87]	<0.0001	0%	0.32
Albania	1	165	333		0.50 [0.41, 0.60]	<0.0001	-	-
Czech Republic	1	80	359		0.91 [0.71, 1.16]	0.45	-	-
Finland	1	NA	NA		0.98 [0.94, 1.02]	0.34	-	-
Hong Kong	1	37	49		0.97 [0.63, 1.49]	0.89	-	-
Hungary	1	54	111		0.95 [0.69, 1.32]	0.76	-	-
Mexico	1	36	53		0.68 [0.45, 1.04]	0.07	-	-
New Zealand	1	361	2,740		0.66 [0.59, 0.74]	<0.0001	-	-
Portugal	1	60	72		0.83 [0.59, 1.17]	0.29	-	-
Saudi Arabia	1	28	16		1.75 [0.94, 3.23]	0.08	-	-
Serbia	1	31	56		0.55 [0.35, 0.85]	0.008	-	-
Spain	1	19	29		0.87 [0.49, 1.55]	0.64	-	-
Multinational	3	2,159	7,022		0.72 [0.55, 0.96]	0.02	96%	<0.00001



APME = Asia Pacific and Middle East; NCSA = North-Central-South America; NA = Not Available

Figure 2 Forest plot of studies reporting NSTACS hospitalizations during the COVID-19 peak compared to the reference period in all studies, grouped by world region and by country.

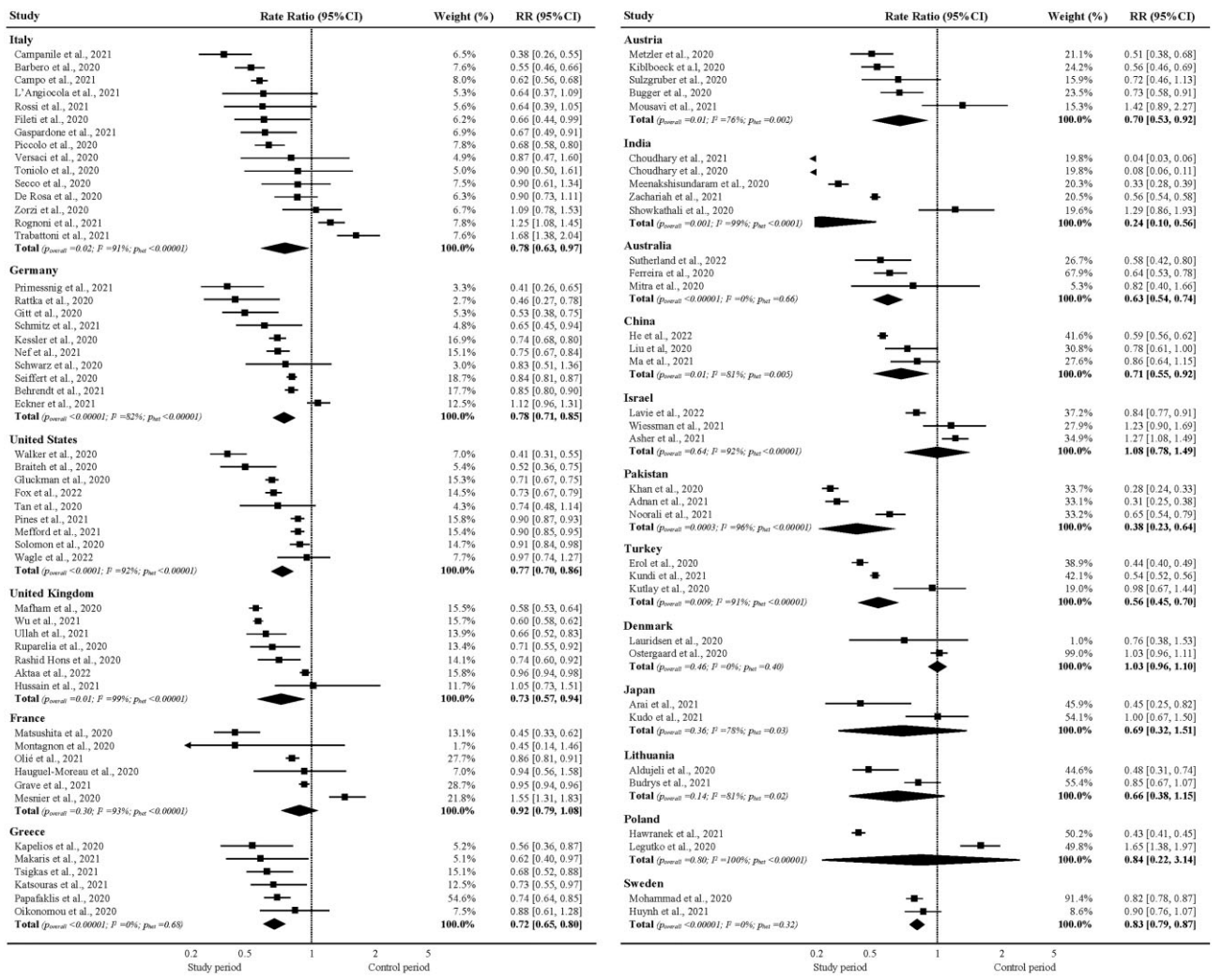


Figure 3 Forest plot of studies reporting NSTACS hospitalizations during the COVID-19 peak compared with the reference period in all studies. Note in many cases the large variability of incidence rate ratio for reports originating from the same country.

Saudi Arabia). Furthermore, in most cases, wide differences could be noticed even for reports originating within the same country (*Figure 3*). Low or no heterogeneity (I^2 < 50%) was observed only for Greece, Australia, Denmark, and Sweden.

Subgroup analyses and publication bias

Stratifying the studies according to many variables to detect possible sources of heterogeneity did not indicate significant differences with respect to type of reporting ('ad hoc' surveys vs. registries), length of observation period, and study quality. Instead, IRR for NSTACS hospitalization was affected by the choice of control period, as studies that used as reference different periods within the same year reported much greater decrease (IRR: 0.61; CI: 0.53–0.71), while data from studies comparing the same periods of 2020 vs. previous years showed substantial less effect (IRR: 0.74; CI: 0.69–0.79) (Supplementary material online, *Table S4*).

Possible presence of publication bias among studies was assessed through funnel plot estimate of effect size vs. standard error, which reported an asymmetrical visual examination (Supplementary material online, *Figure S2*).

Other contributing factors

We also analysed a series of candidate predictor variables as potential contributors to the heterogeneity observed in NSTACS hospitalization rate among countries (*Figure 4*, Supplementary material online, *Table S5*). The most important predictors were: SARS-CoV-2 reproduction rate (RVI 0.996), number of study sites queried (RVI 0.945), and length of reference period (RVI 0.862). Among candidate effect modifiers, the final meta-regression model included only predictors that, among all possible combinations, had RVI values greater than 0.8 (*Table 2*). Of note, stringency index, COVID-19 cases/million, gross domestic product, and other candidate effect modifiers had importance values <0.5, and thus did not significantly contribute to the multiple meta-regression model fit (*Figure 4*, Supplementary material online, *Table S5*).

Discussion

In this study, through a detailed search of published material, we demonstrate on a large geographical scale involving 40 countries in all continents with a total of 553 631 cases that NSTACS hospitalizations significantly decreased during the COVID-19 pandemic compared to

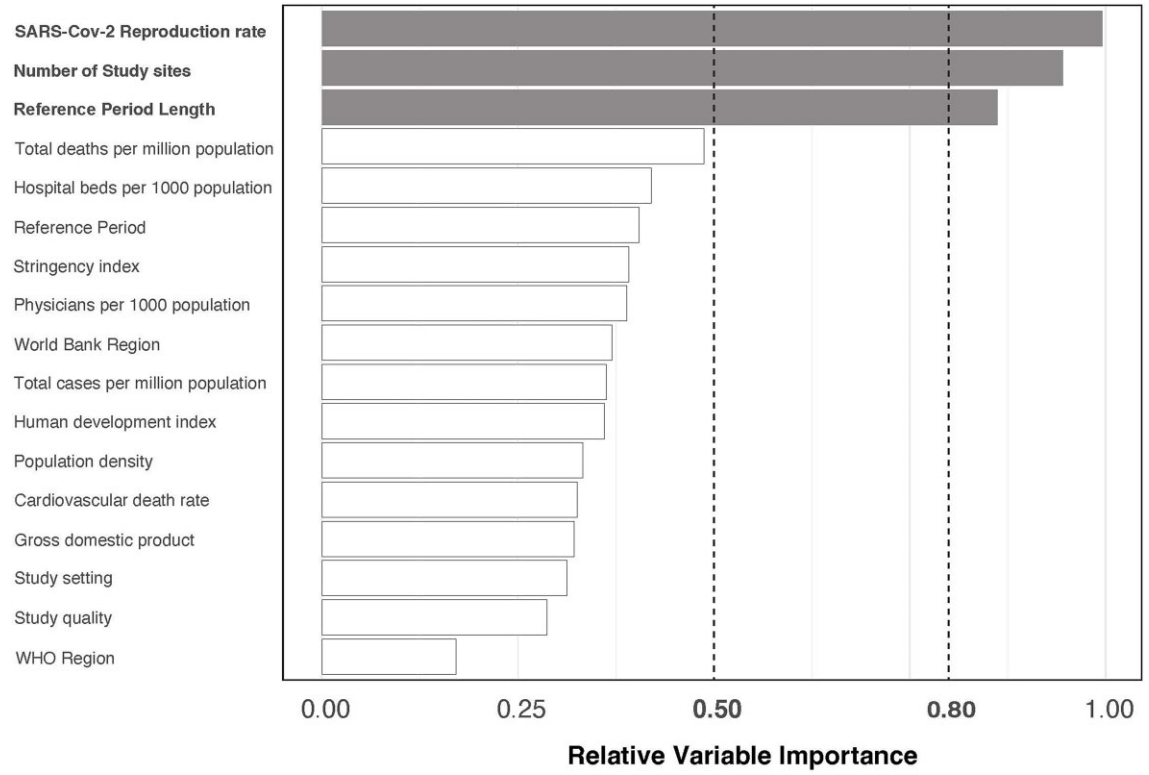


Figure 4 The RVI of model terms. A sufficiently high RVI (>0.5 or 0.8—dashed vertical line) is taken as evidence that a specific moderator is valuable for inference (see text for details).

previous years, by 30% on the average, but with marked heterogeneity among countries and within countries. Furthermore, our observations provide novel insights into this variability of results.

Analysing the impact of COVID-19 on acute coronary syndromes (ACSs) is a relevant issue. Several features of SARS-CoV-2 infection would have predicted that COVID-19 could be associated with increased incidence of ACS, including evidence of intravascular coagulation, prothrombotic autoantibodies, platelet activation, and SARS-CoV-2 localization in the endothelium and vasculitis.[31–37] Indeed, the large Swedish registry of COVID-19 has documented a several-fold increase in the incidence of acute myocardial infarction in the first weeks after infection.[8]

Thus, it might have been expected ACSs hospitalizations to soar during the COVID-19 pandemic. Instead, STEMI hospitalizations actually decreased worldwide.[9,10] As for NSTACS, accounts had provided conflicting results, hospitalizations being reported everywhere from >50% less, to actually more than previous years.[14–16,21–24] However, those discrepant findings were not always based on a rigorous evaluation of evidence, as many derived from surveys obtained 'on the go' over a short period of time, or from just one or a few hospitals.

In addition, the COVID-19 pandemic has put health systems under much pressure to cope with the surge of patients with severe respiratory impairment needing intensive care beds; in some countries this might have affected ability to deliver care to patients with other acute medical illnesses.[38,39] It has also been speculated that health warnings making patients fearful of infection, or overobedience to 'stay-at-home' orders, unintentionally resulted in many patients not presenting to the hospital.[40–42] These, and other factors possibly contributing to the disparate reporting of NSTACS hospitalizations, also need to be accounted for.

Table 2 Final meta-regression model: significant effect modifiers in the final multiple meta-regression model

Covariate	IRR	95% CI	*P*-value
Reproduction rate (R0)	0.380	(0.233–0.618)	<0.001
Reference period length			
Same	Ref.		
Longer	1.449	(1.107–1.897)	0.007
Number of study sites			
1 unit*	Ref.		
2–10 units	0.706	(0.488–1.022)	0.065
11–20 units	0.915	(0.614–1.364)	0.662
>20 units	2.204	(1.424–3.411)	<0.001

Test of moderators effect: $F = 7.23$, P-value < 0.001.
Proportion of heterogeneity accounted for: 25.93%.
Test for residual heterogeneity: $Q = 1903.26$, P-value < 0.001.

These considerations indicate the need for a thorough assessment of the impact of the COVID-19 pandemic on NSTACS hospitalizations, and of factors affecting this process. In addition to understanding the consequences of SARS-CoV-2 infection at the level of individual

patients, investigating these issues can also be of value to recognize, and prevent, consequences of possible future pandemics on proper health delivery and overall health care organization strategies.

Through a systematic review of available evidence, coupled with analysis of many possible contributing factors, our study provides several new insights that may help clarifying the controversy. First, we could establish that NSTACS hospitalizations during the COVID-19 pandemic did significantly decrease worldwide, by 30% on the average. However, looking across countries, we found that the effect of the COVID-19 pandemic on NSTACS hospitalizations was largely heterogeneous, and at times almost opposite (i.e. from >70% decrease to about 10% increase). At a multi-national level, substantial differences emerged among different geographical areas, European countries and North–Central–South America region being least affected, while Asia-Pacific/Middle East reported the most decrease in hospitalization. Of many variables analysed, heterogeneity among countries was significantly influenced by SARS-CoV-2 reproduction rate; instead, other factors often invoked as possible confounders, including total number of COVID-19 cases, severity of social containment measures, or gross domestic product, did not significantly contribute.

Finally, when our analysis delved into evaluating reports from within individual countries, large differences also appeared among country-specific reports (e.g. for Italy IRR for NSTACS hospitalizations went from 0.25 to 1.68; *Figure 3*). Factors possibly influencing the accuracy of reporting did not contribute to local discrepancies; e.g. similar decrease in NSTACS hospitalizations was seen regardless of data type (surveys vs. registries). However, interesting observations might be made concerning differences in the methodology of data acquisition. In fact, significantly lower IRR for NSTACS hospitalizations was seen in reports based on a narrower length of observation period, whereas broader observation periods were associated with modest decrease in IRR, suggesting that a wider accrual base tended to minimize variations. Similarly, another important factor—not previously highlighted—was the referral base upon which the reports were based, as decreased NSTACS hospitalization was more frequently seen in reports involving just a few hospitals, whereas studies based on >20 hospitals actually showed NSTACS admissions higher than previous years.

The finding that the number of hospitals involved in each study influenced the reported impact of COVID-19 on STACS hospitalizations is of particular interest. This observation does not simply reinforce the obvious notion that accuracy of data is influenced by the size of the cohort: More importantly, it provides another clue to interpret the huge variability of different reports, even within a given country (where a number of other factors ought to stay the same). In some countries, many hospitals had been designated 'COVID-only', admitting only COVID-positive patients and shunting away all other patients, whereas other hospitals had been granted 'COVID-free' status, thus admitting also patients with acute conditions usually referred to other hospitals. Consequently, data from either type of hospital may have shown disproportionately lower, or higher, admissions for NSTACS than previous years, just because of this change in admission strategy, either way affecting historical comparison of NSTACS admissions. Different implementation of this policy across countries, or variable sampling of such hospitals across reports, may have affected the results of some surveys.

A recent study described the impact of COVID-19 on various cardiovascular outcomes in many countries.[10] With regard to NSTACS, similar to that study, we also found ~30% decrease in hospitalizations. However, our data substantially extend those observations. First, our meta-analysis is based on a twice larger set of data, as we analysed 104 publications (vs. 52), totalling 111 458 NSTACS cases during the COVID-19 pandemic (vs. 59 369). Second, we specifically analysed additional factors not taken into account previously, including total SARS-CoV-2 cases, stringency index, and number of physicians, which often had been invoked to explain the unexpected decrease in NSTACS hospitalizations and the heterogeneity among countries. Finally, also not previously reported are the findings of a significant impact on NSTACS hospitalizations of SARS-CoV-2 reproduction rate, and of the importance of number of hospitals and length of observation upon which surveys are based.

It is interesting to compare the findings of the present study about NSTACS with a recent report in which we applied a similar approach to investigate the impact of COVID-19 on STEMI hospitalizations.[9] Important similarities—but also differences—emerge. Also in the case of STEMIs, we documented that the decrease in hospital admission was not uniform across countries, as many showed a significant decrease in STEMI hospitalizations, and other negligible decrease or even increase. Also similar were the findings regarding the lack of impact of type (surveys vs. registries), or quality of reports, which did not contribute to the observed heterogeneity. In contrast, we now describe a significant impact of SARS-CoV-2 reproduction rate in affecting NSTACS hospitalizations, which was not evident with respect to STEMI hospitalizations. Our meta-analysis cannot establish reasons behind the different effects of certain variables on NSTACS compared with STEMI hospitalizations. However, some tentative explanations can be advanced. For one thing, unlike STEMI, diagnosis of NSTACS is not always immediately evident and its symptoms are often less relevant. Thus, it is conceivable that some NSTACS patients were not identified as such, or that patients themselves did not seek immediate medical advice. This may have resulted in some patients staying at home or being routed to intensive care units or general wards, which, however, were working at capacity because of COVID-19 patient load.[38–40] The finding that NSTACS were more affected compared to STEMI hospitalizations, and the inverse relationship of NSTACS hospitalization with SARS-CoV-2 replication rate, might indicate that medical attention, resources, and patients' perception were geared towards COVID-19 or anyhow other clearly perceived life-threatening conditions, while some patients suffering from other (yet quite serious) conditions might have stayed home, because of paucity of hospital resources, or due to patients fearing the risk of SARS-CoV-2 infection.

Limitations

Our analysis encompassed 2020. While we cannot comment whether COVID-19 may have affected NSTACS hospitalization subsequently, this might be considered a strength, as data refer to a relatively uniform condition, since the strain of the SARS-CoV-2 virus was the same in all countries and no virus variants had appeared yet, and at a time when there was still no vaccine available that may have influenced the disease.

Conclusions

This large meta-analysis shows that hospitalizations for NSTACS decreased significantly during the COVID-19 pandemic, worldwide. However, the magnitude of the phenomenon showed very large differences among countries, and substantial heterogeneity emerged even within the same country. Factors linked to the spread of SARS-CoV-2 infection, but also to methodologies to obtain the results may have contributed to this heterogeneity.

Collectively, these considerations indicate that public health strategies and overall health care organization to cope with a pandemic may be an issue of concern deserving further investigation[43]; decisions, however, must be based on solid data, not on brief reports hastily obtained in the midst of a pandemic.

Supplementary material

Supplementary material is available at *European Heart Journal—Quality of Care and Clinical Outcomes* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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