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REVIEW

Systematic review and meta-analysis of the characteristics and outcomes of readmitted COVID-19 survivors

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Key words
readmission, COVID-19, rehospitalisation, mortality, systematic review, re-presentation.

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Abstract

The objective of the present study is to investigate the incidence, characteristics and outcomes of patients who were readmitted to hospital emergency departments or required re-hospitalisation following an index hospitalisation with a diagnosis of COVID-19. A systematic review of PubMed, EMBASE and pre-print websites was conducted between 1 January and 31 December 2020. Studies reporting on the incidence, characteristics and outcomes of patients with COVID-19 who represent or require hospital admission were included. Two authors independently performed study selection and data extraction. Study quality was assessed with the Newcastle-Ottawa Scale. Discrepancies were resolved by consensus or through an independent third reviewer. Data were synthesised according to the Preferred Reporting Items for Systematic Reviews guidelines. Six studies reporting on 547 readmitted patients were included. The overall incidence was 4.4%, most common in males (57.2%), and due to respiratory distress or prolonged COVID-19. Readmitted patients had a shorter initial hospital length of stay (LOS) compared with those with a single hospitalisation (8.1 $\pm$ 10.6 vs 13.9 $\pm$ 10.2 days). The mean time to readmission was 7.6 $\pm$ 6.0 days; the mean LOS on re-hospitalisation was 6.3 $\pm$ 5.6 days. Hypertension (odds ratio (OR) = 2.08; 95% confidence interval (CI) 1.69–2.55; $P < 0.001$; $I^2 = 0\%$), diabetes mellitus (OR = 1.77; 95% CI 1.38–2.27; $P < 0.001$; $I^2 = 0\%$) and chronic renal failure (OR = 2.37; 95% CI 1.09–5.14; $P < 0.001$; $I^2 = 0\%$) were more common in these patients. Intensive care admission rates were similar between the two groups; 12.8% (22/172) of readmitted patients died. In summary, readmitted patients following an index hospitalisation for COVID-19 were more commonly males with multiple comorbidities. Shorter initial hospital LOS and unresolved primary illness may have contributed to readmission.

Introduction

The Coronavirus disease 2019 (COVID-19) pandemic, caused by the highly transmissible severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to be a worldwide health crisis, with many countries facing repeated surges in positive COVID-19 cases, resulting in a rise in hospitalisations and ongoing strain on the healthcare system.[1] The clinical manifestation and outcomes of patients infected with COVID-19 vary widely.[2] While the risk factors and characteristics of patients with COVID-19 requiring hospitalisation are well documented, data pertinent to readmission rates in survivors are limited. Disease-specific data on the outcomes for re-hospitalised patients with COVID-19 are essential to properly inform guidelines. Therefore, we conducted a rapid review to evaluate the incidence, characteristics and outcomes of patients who re-presented to hospital emergency departments or required readmission following an index hospitalisation with a diagnosis of COVID-19.

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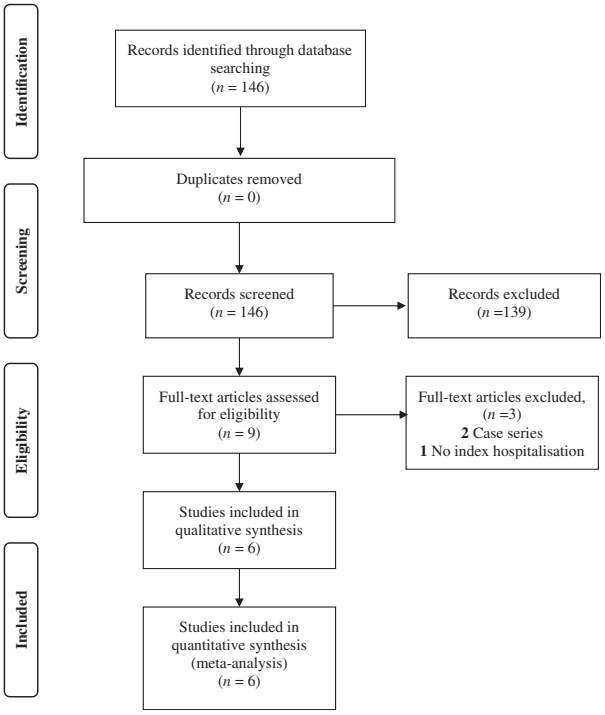


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) consort flow diagra illustrating inclusion of studies for qualitative and quantitative analysis.

Methods

The present study was conducted in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[3] Figure 1 illustrates the consort flow diagram. We adopted the validated 'rapid review' methodology[4] while carrying out a literature search and pursuing through the relevant articles.

Eligibility criteria

Studies reporting on the incidence, characteristics and outcomes of consecutive patients with COVID-19 who represent or require hospital admission were included.

Search strategy, information sources and study selection

Two authors (ZJL and AS) independently searched the publicly available COVID-19 living systematic review.[5] This living systematic review is updated daily and provides a dynamic database of research papers related to COVID-19 that are indexed by PubMed, EMBASE, MedRxiv, and BioRxiv. This has been validated in previously published COVID-19-related research.[6] Due to the rapidly evolving pandemic, preprint studies that were yet to be peer reviewed were included to capture as much data as possible. Studies were extracted between 1 January and 31 December 2020, using the search terms, 're-admission', 're-present' and 're-admit' with and without hyphenation within the title and the abstract columns of the systematic review list. These terms were combined with the Boolean operator 'OR'. Preprint and non-English language articles were included. The bibliography of each study was analysed to identify studies that may have been missed during the literature search.

Quality assessment and risk of bias in individual studies

The Newcastle-Ottawa Scale (NOS) is a quality assessment tool used to evaluate non-randomised studies based on an eight-item score divided into three domains.[7] These domains assess selection, comparability and ascertainment of the outcome of interest. The Newcastle-Ottawa Scale was used by the two reviewers (ZJL, MR) to independently evaluate the quality of included studies and assess for risk of bias. The same set of decision rules was used by each reviewer to score the studies. Any discrepancies from the NOS were reviewed and resolved by a third author (AS).

Data collection and analysis

Statistical analyses were conducted using Review Manager 5.4 (2020; The Cochrane Collaboration, London, UK). To enable an analysis of results between studies, median values were converted to means through an estimation formula (Supporting Information Table S1).[8] Categorical variables are presented as percentages, with between-group differences compared using Fisher's exact tests. A two-tailed *P*-value <0.05 was considered significant. Equality of two proportions was evaluated using the *Z*-test. The pooled prevalence and odds ratios (OR) were calculated across studies using random-effects models of restricted maximum-likelihood method. In the presence of heterogeneity (as expected and observed), random-effect models have superior properties and are more conservative than fixed-effect models.[9] Heterogeneity across the studies was evaluated using the Cochran Q test and quantified using I^2 statistic. Heterogeneity among studies was categorised as high (I^2: 76–100%), moderate (I^2: 26–75%) and low (I^2: 0–25%).[10] Subgroup analyses and meta-regression were not conducted to explore the possible reasons of heterogeneity due to the relatively small number of studies and patients.

Results

A total of 146 studies were obtained from the living systematic review, with six studies across five countries (USA, South Korea, Spain, UK and Turkey) were included for qualitative and statistical analysis.[11–16] All studies were graded fair (Table S2).

The incidence, characteristics and outcomes across these studies are detailed in Table 1. The forest plots analysing gender and intensive care unit (ICU) admission is illustrated in Figure 2. A total of 547 patients with COVID-19 re-presented to emergency or required hospital readmission, representing an overall incidence of 4.4%. Most (52.5%) patients were re-hospitalised due to respiratory distress or prolonged COVID-19, which is due to lingering symptoms recurring disease after initial recovery.[11,13–16] Mean age was similar at 65.2 ± 16.4 years among patients who had a single admission

Table 1 Selected studies

	Atalla *et al.*[11]	Jeon *et al.*[12]	Parra *et al.*[13]†	Rokadiya *et al.*[15]	Uyaroğlu *et al.*[16]	Somani *et al.*[14]	Total, *n* (%, 95% CI)
Location	Rhode Island, USA	South Korea	Madrid, Spain	London, UK	Ankara, Turkey	New York, USA	—
Newcastle Ottawa Scale‡	Fair	Good	Good	Fair	Good	Fair	—
Sample size							
Nil readmission	320	7262	61†	391	143	2761	12021§
Readmission	19	328	61	25	11	103¶	547
Readmission rate (%)	5.6	4.3	5.1	6.0	7.1%	3.6	4.4
Age, median (IQR) (years)							
Nil readmission	61 (49–74)	NR	66 (57–76)	59 (48–76)	44 (NR)	65.9 (54.5–77.0)	—
Readmission	58 (44–69)	NR	67 (59–76)	73 (58–82)	49 (NR)	66.1 (53.7–75.1)	—
Age, derived mean (SD) (years)							
Nil readmission	61.3 (18.6)	NR	66.3 (14.4)	61.0 (20.8)	NR	65.8 (16.9)	65.2 (16.4)
Readmission	57.0 (20.0)	NR	67.3 (12.9)	71.0 (18.9)	NR	65.0 (16.1)	65.7 (16.2)
Male, *n* (%)							
Nil readmission	179 (55.9)	2925 (40.3)	45 (73.8)	NR	71 (49.7)	1598 (57.9)	4818/10547 (45.7, 44.7–46.6)
Readmission	12 (63.2)	170 (51.8)	45 (73.8)	15 (60.0)	6 (54.5)	65 (63.1)	313/547 (57.2, 53.0–61.4)
Congestive heart failure, *n* (%)							
Nil readmission	30 (9.4)	44 (0.6)	NR	NR	7 (4.9)	NR	240/10486 (2.3, 2.0–2.6)
Readmission	2 (10.5)	3 (0.9)	NR	NR	0 (0.0)	NR	13/461 (2.8, 1.5–4.8)
Ischaemic heart disease, *n* (%)							
Nil readmission	NR	143 (2.0)	12 (19.7)	NR	NR	220 (8.0)	375/10084 (3.7, 3.4–4.1)
Readmission	NR	7 (2.1)	16 (26.2)	NR	NR	12 (11.7)	35/492 (7.1, 5.0–9.8)
Hypertension, *n* (%)							
Nil readmission	141 (44.1)	890 (12.3)	24 (39.3)	NR	20 (14.0)	610 (22.1)	1685/10547 (16.0, 15.3–16.7)
Readmission	13 (68.4)	73 (22.3)	34 (55.7)	16 (64.0)	5 (45.5)	36 (35.0)	177/547 (32.4, 28.5–36.5)
Diabetes mellitus, *n* (%)							
Nil readmission	103 (32.2)	558 (7.7)	10 (16.4)	NR	17 (11.9)	420 (15.2)	1108/10547 (10.5, 9.9–11.1)
Readmission	11 (57.9)	46 (14.0)	14 (23.0)	6 (24.0)	2 (18.2)	19 (18.4)	98/547 (17.9, 14.8–21.4)
Obesity, *n* (%)							
Nil readmission	125 (39.1)	NR	5 (8.2)	NR	NR	NR	130/381 (34.1, 29.4–39.1)
Readmission	10 (52.6)	NR	6 (9.8)	NR	NR	NR	16/80 (20.0, 11.9–30.4)
COPD/asthma, *n* (%)							
Nil readmission	41 (12.8)	712 (9.8)	12 (19.7)	NR	13 (9.1)	NR	778/7786 (10.0, 9.3–10.7)
Readmission	11 (57.9)	42 (12.8)	12 (19.7)	NR	0 (0.0)	NR	65/419 (15.5, 12.2–19.3)
Chronic renal failure, *n* (%)							
Nil readmission	32 (10.0)	38 (0.5)	NR	NR	NR	NR	70/7582 (0.9, 0.7–1.2)
Readmission	4 (21.1)	4 (1.2)	NR	NR	NR	NR	8/347 (2.3, 1.0–4.5)
Liver disease, *n* (%)							
Nil readmission	8 (2.5)	341 (4.7)	NR	NR	NR	NR	349/7582 (4.6, 4.1–5.1)
Readmission	3 (15.8)	11 (3.4)	NR	NR	NR	NR	14/347 (4.0, 2.2–6.7)
Cancer, *n* (%)							

Table 1 *Continued*

	Atalla *et al.*[11]	Jeon *et al.*[12]	Parra *et al.*[13]†	Rokadiya *et al.*[15]	Uyaroğlu *et al.*[16]	Somani *et al.*[14]	Total, *n* (%, 95% CI)
Nil readmission	23 (7.2)	266 (3.7)	12 (19.7)	NR	3 (2.1)	NR	304/7786 (3.9, 3.5–4.4)
Readmission	4 (21.1)	16 (4.9)	12 (19.7)	NR	2 (18.2)	NR	34/419 (8.1, 5.7–11.2)
ICU admission, *n* (%)							
Nil readmission	110 (34.4)	758 (10.4)	5 (8.2)	NR	NR	524 (19.0)	1397/10404 (13.4, 12.8–14.1)
Readmission	6 (31.6)	38 (11.6)	3 (4.9)	2 (8.0)	NR	6 (5.8)	55/511 (10.8, 8.2–13.8)
Mechanical ventilation, *n* (%)							
Nil readmission	64 (20.0)	NR	NR	NR	NR	293 (10.6)	357/3081 (11.6, 10.5–12.8)
Readmission	3 (15.8)	NR	NR	NR	NR	1 (0.97)	4/122 (3.3, 0.9–8.2)
Hospital length of stay, median (IQR) (days)							
Nil readmission	8 (4–15)	17 (10–24)	9 (6–14)	7 (4–11)	4 (1–28)	6.7 (3.5–11.5)	—
Readmission††	6 (3–12)	9 (1–18)	6 (4–14)	6 (1–9)	3 (2.5–5.5)	4.7 (2.9–9.1)	—
Time to readmission	5 (3–13)	NR	6 (3–10)	10 (6–15)	8 (4–11.5)	4.5 (NR)	—
Readmission‡‡	7 (4–9)	NR	NR	NR	3 (1.5–4)	NR	—
Hospital length of stay, derived mean (SD) (days)							
Nil readmission	9 (8.2)	17 (10.4)	9.7 (6.1)	7.3 (5.2)	9.3 (5.1)	7.2 (5.9)	13.9 (10.2)
Readmission††	7 (5.6)	9.3 (12.7)	8 (7.6)	5.3 (6.3)	5.5 (6.9)	5.6 (4.7)	8.1 (10.6)
Time to readmission	7.7 (6.1)	NR	6.3 (5.3)	10.3 (7.1)	8.2 (5.2)	NR	7.6 (6.0)
Readmission‡‡	7.9 (6.1)	NR	NR	NR	3.5 (3.0)	NR	6.3 (5.6)
Reason for admission, *n* (%)							
Respiratory distress/ prolonged COVID-19	8 (42.1)	NR	34 (55.7)	14 (56.0)	8 (72.7)	51 (49.5)	115/219 (52.5, 45.7–59.3)
Cardiac: heart failure, chest pain, AMI	NR	NR	7 (11.5)	NR	NR	6 (5.8)	13/164 (7.9, 4.3–13.2)
Thrombotic episode	2 (10.5)	NR	10 (16.4)	NR	NR	NR	12/80 (15.0, 8.0–24.7)
Fall/trauma	1 (5.3)	NR	NR	NR	NR	5 (4.9)	6/122 (4.9, 1.8–10.4)
Others	8 (42.1)	NR	10 (16.4)	11 (44.0)	3 (27.3)	41 (39.8)	73/219 (33.3, 27.1–40.0)
Outcomes following readmission, *n* (%)							
Death	2 (10.5)	NR	9 (14.7)	6 (24.0)	2 (18.2)	3 (5.4)§§	22/172 (12.8, 8.2–18.7)
Still admitted	1 (5.3)	NR	NR	3 (12.0)	0 (0.0)	2 (3.6)§§	6/111 (5.4, 2.0–11.4)
Recovered	16 (84.2)	NR	NR	16 (64.0)	9 (81.8)	51 (91.1)§§	92/111 (82.9, 74.6–89.4)

†Parra *et al.*13 reported a matched (1:1) cohort. A total of 1144 patients had an initial admission but no hospital readmission.
‡Please refer Table S2 for Individual study quality by NOS score that was performed independently by two authors.
§Total includes 1144 patients from Parra *et al.*,14 who had an initial admission but no hospital readmission.
¶Among 103 patients who re-presented to hospital.
††Length of stay during first hospital admission.
‡‡Length of stay during second hospital admission.
§§Among 56 patients who were admitted to hospital.
AMI, acute myocardial infarction; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.

compared with 65.7 ± 16.2 years among patients who were re-hospitalised. There were more male patients in the readmission group (57.2%, 95% CI 53.0–61.4) than those who had a single admission (45.7%; 95% CI 44.7–46.6; OR = 1.46; 95% CI 1.22–1.76; $P < 0.001$). Among patients with a single hospital admission, mean hospital length of stay (LOS) was 13.9 ± 10.2 days, compared with 8.1 ± 10.6 days among patients who had a subsequent hospital admission. All six studies reported a shorter hospital LOS among patients who were re-hospitalised. The mean time to re-hospitalisation was 7.6 ± 6.0 days among patients who were readmitted to hospital following hospital discharge. Mean LOS during the second admission was 6.3 ± 5.6 days.

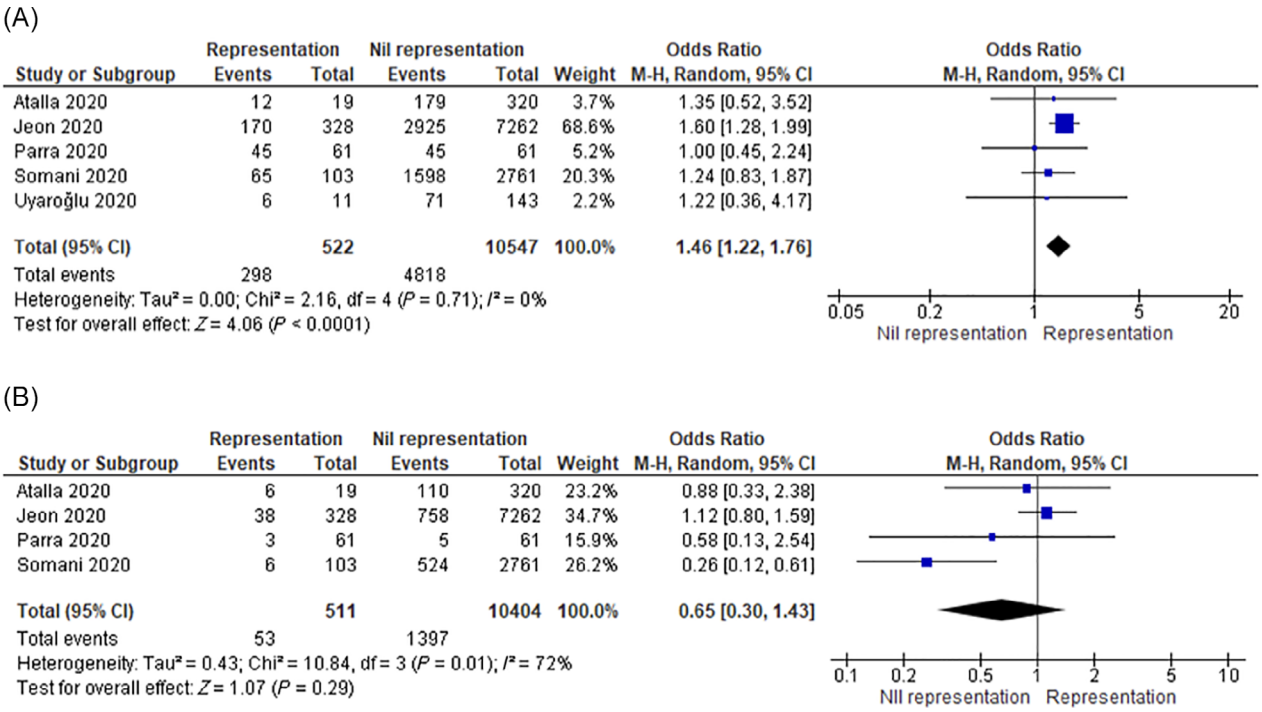


Figure 2 Forest plots representing characteristics in (A) male patients and (B) intensive care unit (ICU) admission. CI, confidence interval.

When analysing the comorbidities in patients who were readmitted in comparison to those who had a single admission, the frequency of ischaemic heart disease, hypertension, diabetes mellitus, chronic obstructive pulmonary disease or asthma, and cancer were higher and statistically significant among patients who were re-hospitalised. Hypertension (OR = 2.08; 95% CI 1.69–2.55; $P < 0.001$; $I^2 = 0\%$), diabetes mellitus (OR = 1.77; 95% CI 1.38–2.27; $P < 0.001$; $I^2 = 0\%$) and chronic renal failure (OR = 2.37; 95% CI 1.09–5.14; $P < 0.001$; $I^2 = 0\%$) were significantly more frequent among patients who were readmitted (Table 1, Fig. 3). The frequency of ICU admission was similar between both groups (OR = 0.65; 95% CI 0.30–1.43; $P = 0.29$) (Fig. 2). Across five studies, a total of 22 (12.8%) of 172 patients died following readmission.[11,13–16]

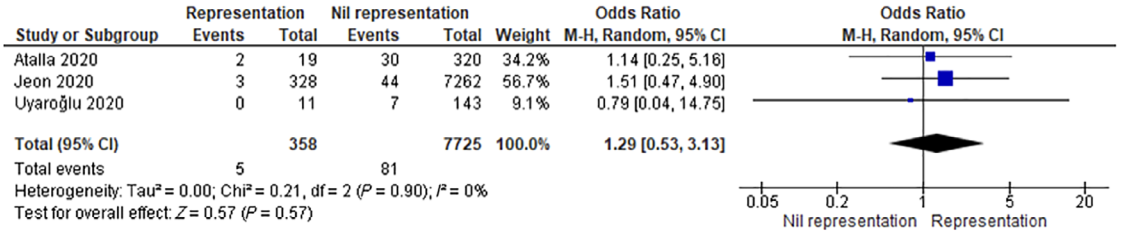
Discussion

This is the first systematic review to examine the incidence, characteristics and outcomes of patients who re-present to hospital following initial hospital discharge. Overall, patients who re-presented were more likely male, and suffer from various comorbidities with hypertension, chronic renal failure and cancer being the most common.

Notably, patients who re-presented to the hospital had an overall shorter initial hospital LOS, with COVID-19-related respiratory symptoms as the most common reason for re-presentation. The reason for readmission may be due to an unresolved primary illness, potentially premature hospital discharges in the context of significant demand for hospital beds due to a surge in patients with COVID-19,[17] limited patient care post-discharge,[14] or repeat manifestation of disease again with symptoms or redetection following repeat testing.[12] Long-term rehabilitation care for COVID-19 survivors may aid in reducing both the incidence and mortality following hospital representation.[18]

The overall hospital re-presentation rate of 4.4% was lower compared with studies investigating the readmission rate for patients with seasonal influenza, where the readmission rate ranged from 10.2 to 14%.[19,20] This could be due to either saturated hospitals bed capacity or hospitals limiting admissions to preserve resources and limit exposure risk. In contrast, the mortality rate of 12.8% reported in this review was considerably higher when compared with 6.5–7% among patients with influenza.[19,20] In keeping with our findings, a recent study also identified the re-hospitalisation rates or death were higher among patients with COVID-19 than those with pneumonia or heart failure during the first 10 days after discharge following COVID-19 hospitalisation, suggesting a period of heightened risk of clinical deterioration.[21] While the exact reason for the higher mortality rate is unclear, the potential biphasic illness course of COVID-19 may have contributed to the increased mortality.[22]

(A)



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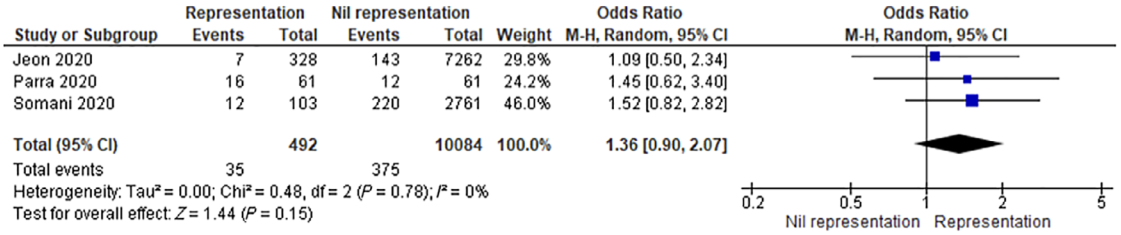

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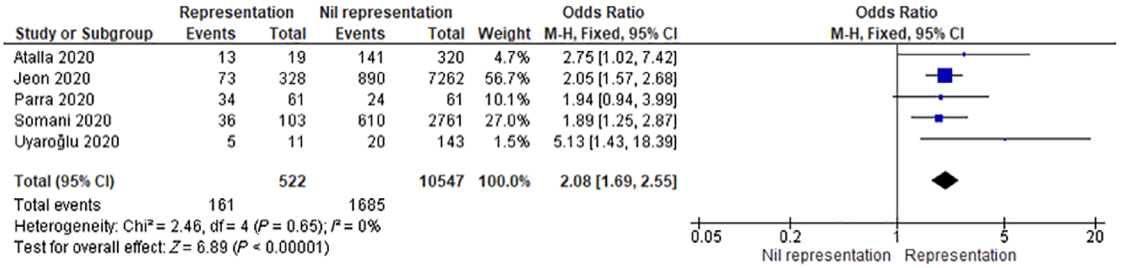

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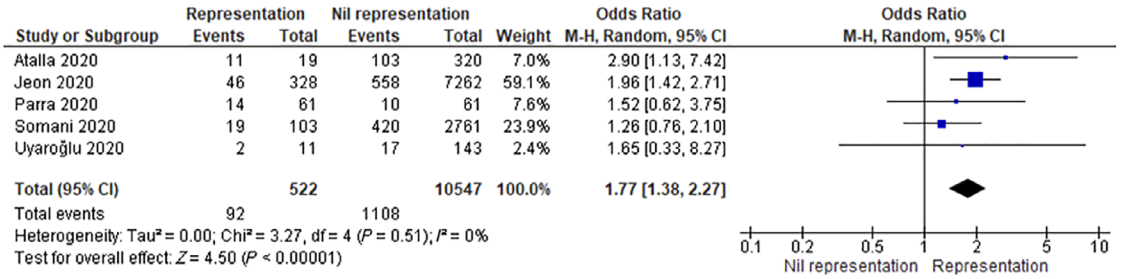

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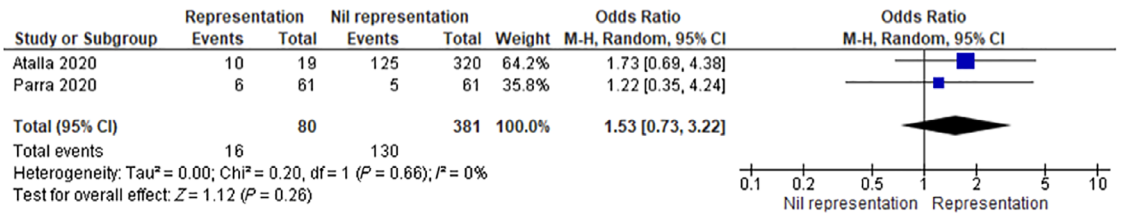
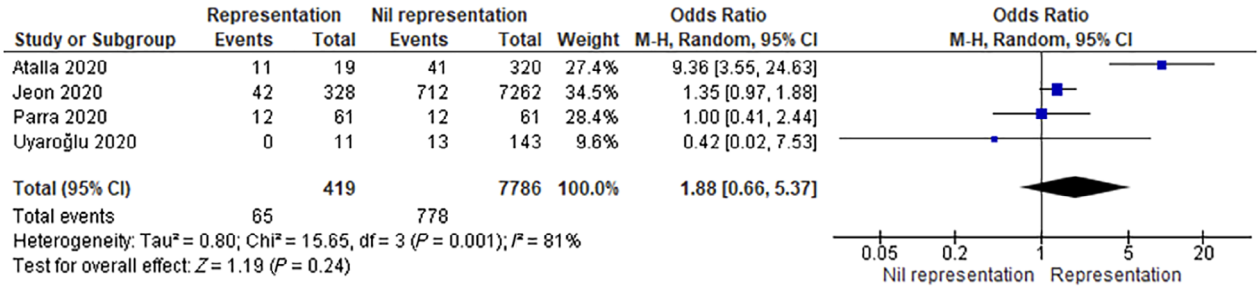
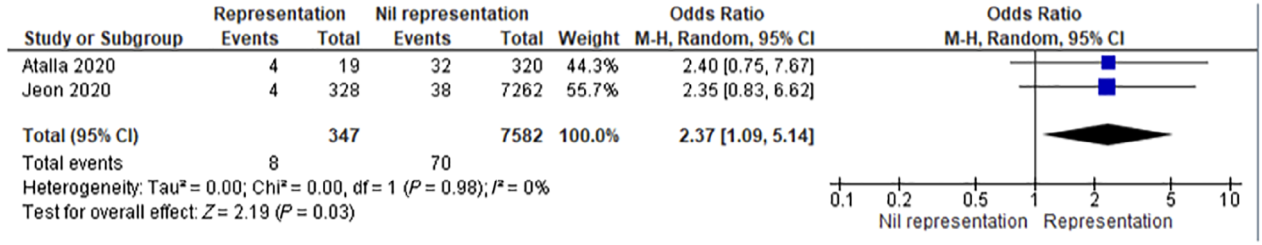


Figure 3 Forest plots comparing the comorbidities among patients who were readmitted compared with those with a single indexed admission. (A) Congestive heart failure; (B) ischaemic heart disease; (C) hypertension; (D) diabetes; (E) obesity; (F) chronic obstructive pulmonary disease (COPD)/asthma; (G) renal failure; (H) liver disease; and (I) cancer. CI, confidence interval.

(F)



(G)



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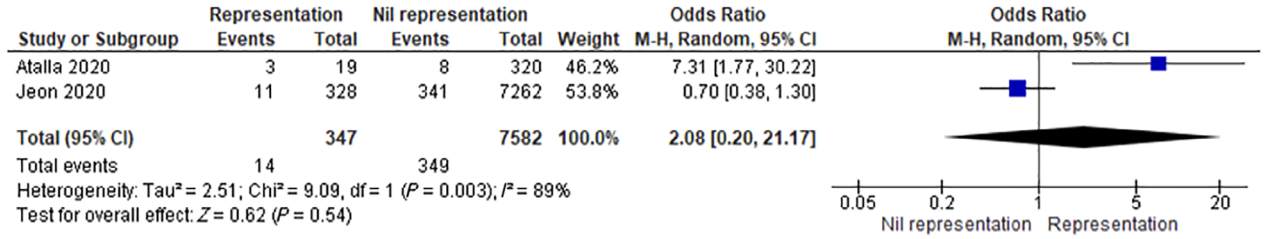

(I)

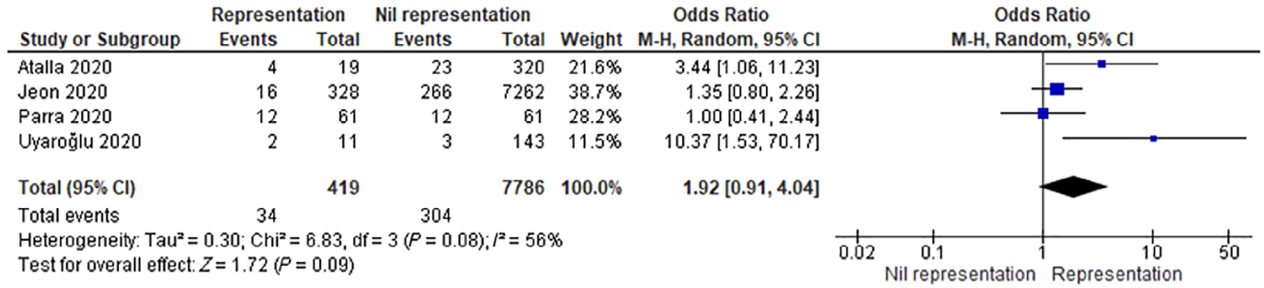

Figure 3 Continued.

The present study has a few limitations that need to be addressed. First, the lack of age and disease stratification of COVID-19, and overall small sample size of patients who were re-hospitalised. Second, we could not describe the pooled difference of in-hospital mortality between the patients with COVID-19 who were re-hospitalised with those patients who had a single admission. Additionally, the eventual outcome of patients who had one admission was not investigated in this review, where they may have died prior to re-hospitalisation or presented to another hospital where the readmission was not captured in the reported study. The analysed re-presentation time period was variable among

studies, ranging 14−30 days. A more consistent evaluation over a 30-day re-presentation period is needed to effectively compare the re-presentation rates with other known diseases.

Conclusion

This review identified that patients with COVID-19 who re-present to hospital following an index hospitalisation for COVID-19 were more likely to be of male sex and suffer multiple comorbidities. Even though the re-presentation rate was lower than that reported for seasonal influenza, mortality was much higher. Shorter initial hospital LOS and unresolved primary illness may have contributed to re-presentation. Equally, patients might be presenting late, which leads to the higher mortality. Future studies are required to examine the reasons behind the higher mortality rate seen in patients who re-present to hospitals following an index admission of COVID-19.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Table S1 Equation used to calculate mean and standard deviation from median and interquartile range.
Table S2 Individual study quality by Newcastle Ottawa Scale (NOS) score.