American Journal of Emergency Medicine 51 (2022) 267–279

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Hospital readmissions and post-discharge all-cause mortality in COVID-19 recovered patients; A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 8 September 2021
Received in revised form 27 October 2021
Accepted 28 October 2021

Keywords:
Hospital readmission
COVID-19
Re-infection
Mortality

ABSTRACT

Objective: The present study aimed to perform a systematic review and meta-analysis on the prevalence of one-year hospital readmissions and post-discharge all-cause mortality in recovered COVID-19 patients. Moreover, the country-level prevalence of the outcomes was investigated.
Methods: An extensive search was performed in Medline (PubMed), Embase, Scopus, and Web of Science databases until the end of August 3rd, 2021. A manual search was also performed in Google and Google Scholar search engines. Cohort and cross-sectional studies were included. Two independent reviewers screened the papers, collected data, and assessed the risk of bias and level of evidence. Any disagreement was resolved through discussion.
Results: 91 articles were included. 48 studies examined hospital readmissions; nine studies assessed post-discharge all-cause mortality, and 34 studies examined both outcomes. Analyses showed that the prevalence of hospital readmissions during the first 30 days, 90 days, and one-year post-discharge were 8.97% (95% CI: 7.44, 10.50), 9.79% (95% CI: 8.37, 11.24), and 10.34% (95% CI: 8.92, 11.77), respectively. The prevalence of post-discharge all-cause mortality during the 30 days, 90 days and one-year post-discharge was 7.87% (95% CI: 2.78, 12.96), 7.63% (95% CI: 4.73, 10.53) and 7.51% (95% CI, 5.30, 9.72), respectively. 30-day hospital readmissions and post-discharge mortality were 8.97% and 7.87%, respectively. The highest prevalence of hospital readmissions was observed in Germany (15.5%), Greece (15.5%), UK (13.5%), Netherlands (11.7%), China (10.8%), USA (10.0%) and Sweden (9.9%). In addition, the highest prevalence of post-discharge all-cause mortality belonged to Italy (12.7%), the UK (11.8%), and Iran (9.2%). Sensitivity analysis showed that the prevalence of one-year hospital readmissions and post-discharge all-cause mortality in high-quality studies were 10.38% and 4.00%, respectively.
Conclusion: 10.34% of recovered COVID-19 patients required hospital readmissions after discharge. Most cases of hospital readmissions and mortality appear to occur within 30 days after discharge. The one-year post-discharge all-cause mortality rate of COVID-19 patients is 7.87%, and the majority of patients' readmission and mortality happens within the first 30 days post-discharge. Therefore, a 30-day follow-up program and patient tracking system for discharged COVID-19 patients seems necessary.

1. Introduction

The coronavirus disease 2019 (COVID-19) has become a global pandemic and the statistics are increasing daily. Numerous mutations in the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) have caused an increase in the number of COVID-19 re-infections and related hospital readmissions. There is evidence indicating that these mutations may have reduced the efficacy of current vaccines [1,2]. This re-infection and the decline in immune responses against the SARS-CoV-2 have triggered a re-emergence of the disease in some communities [3,4], bearing in mind that current treatments are not adequately effective in improving the outcome of COVID-19 [5-7].

Re-infection and hospital readmissions are important indicators of controlling the COVID-19 pandemic and healthcare performance quality [8]. Hospital readmissions as a public health concern increase resource utilization and impose an additional burden on the healthcare system [9-11]. At the beginning of the pandemic, studies indicated that recurrence/re-infection of COVID-19 was rare [12,13], but more recent evidence has shown that a significant percentage of patients with COVID-19 develop recurrence of symptoms and require readmission [11,14,15]. The prevalence of hospital readmissions in patients with COVID-19 varies between 1% [16] to 48% [14].

Increasing numbers of recovered COVID-19 patients and their follow-up has shown that that the post-discharge mortality of COVID-19 patients occurs one year after discharge from the index hospitalization. Prevalence of post-discharge mortality of COVID-19 patients was

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https://doi.org/10.1016/j.ajem.2021.10.059
0735-6757/© 2021 Published by Elsevier Inc.

reported between 0% [17] to 37% [18]. However, most studies are single-site researches, and there exists no comprehensive data on post-discharge mortality of recovered COVID-19 patients. There are also significant differences in follow-up time and setting of COVID-19 patients among current studies, making conclusions in this field challenging.

The current systematic review and meta-analysis has investigated the prevalence of hospital readmissions and post-discharge all-cause mortality in follow-up periods of 30 days, 90 days, and one year, to provide comprehensive figures. As a secondary aim, the prevalence of country-level hospital readmissions and post-discharge all-cause mortality has been reported.

2. Method

2.1. Study design

The present study is a systematic review and meta-analysis of observational studies. The protocol of the present study was designed based on Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guideline [19]. The protocol of the current review was not registered and publicly accessed. In all steps, two independent reviewers screened the papers, collected data, and assessed the risk of bias and level of evidence. Any disagreement was resolved through discussion. The agreement rate was 92.3% to 100% for each level of screening and data extraction.

2.2. Eligibility criteria

In the present study, cohort and cross-sectional studies on the prevalence of hospital readmissions and post-discharge all-cause mortality after recovery from COVID-19 were included. Case-control studies were excluded since the nature of sampling in case-control studies overestimates the prevalence of hospital readmissions and post-discharge all-cause mortality. Case reports, duplicate reports, reviews, and pediatric studies were also excluded. Presenting combined data of in-hospital and post-discharge outcomes without any stratification and reporting data on patients discharged from the emergency department without hospitalization in index admission (first admission) were other exclusion criteria. In addition, studies were excluded if they did not assess hospital readmissions or post-discharge all-cause mortality and did not report the total sample size of their COVID-19 patients.

2.3. Search strategy

An extensive search was performed on PubMed, Embase, Scopus, and Web of Science until the end of August 3rd,2021, without time or language limitations. In addition, a manual search was performed on Google and Google Scholar search engines. Since a significant number of COVID-19 papers were accessible as preprints, the manual search was performed cautiously to include relevant preprint articles. The search term is reported in Supplementary material 1.

2.4. Screening and data collection

Records from systematic and manual searches were gathered into EndNote X8.0 software (Clarivate Analytics, Philadelphia, PA, USA), and duplicates were removed. In a two-step process, related articles were selected based on the inclusion and exclusion criteria. In the first step, the titles and abstracts were reviewed and possibly related articles were identified. In the next step, the full texts of the articles were evaluated and related papers were identified and included in the present study. Collected data include study characteristics (name of the first author, year of publication, country), study design (retrospective or prospective), patients' settings, COVID-19 diagnostic criteria, discharge criteria, sample size, age, and gender distribution, underlying diseases, and follow up duration. Underlying disease or infection was defined as the presence of cirrhosis and liver injury, myocardial infarction, cardiovascular disease, autoimmune diseases, cancer, fungal infections, HIV infection, rheumatic and musculoskeletal disease, and acute kidney injury.

2.5. Outcome

The outcomes of interest were hospital readmissions and post-discharge all-cause mortality. Hospital readmissions were defined as the readmission of recovered COVID-19 patients who had previously been hospitalized for COVID-19. Post-discharge all-cause mortality was also considered as all post-discharge deaths in recovered COVID-19 patients.

2.6. Risk of bias assessment

The risk of bias was assessed using National, Heart, Lung, and Blood Institute (NHLBI) tools for cohort and cross-sectional studies [20]. NHLBI risk of bias tools contains 14 signaling questions for the assessment of the quality of included studies (Supplementary Table 1). According to the observational nature of the included studies, participation rate less than 50% (item 3), assessment of exposure prior to outcome assessment (item 6), insufficient timeframe for outcome assessment (item 7), not clear and valid measurement of exposure (item 9) and outcomes (item 11) and more than 20% loss to follow-up (item 13) were defined as fatal errors.

Since most of the studies collected their data from registries, the unblind outcome assessment (item 12) did not have a considerable effect on the quality of the studies. Therefore, unblinded outcome assessment was not considered a fatal error. Sample size calculation was not reported in any of the included studies. Therefore, if the sample size of a study was lower than 100 patients, item 5 was considered as high risk. In addition, item 14 of the NHLBI risk of bias tool was not applicable for this review.

The overall risk of bias was rated as “high” if any concern (high risk; NR or CD) was presented in items 3, 6, 7, 9, 11, and 13 (fatal error). The overall risk of bias was rated as “some concern” if there were no fatal errors and there were a concern (high risk, NR, or CD) in at least two items [21].

2.7. Level of evidence

The level of evidence was determined based on the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework. The GRADE framework classifies the level of evidence for each outcome based on the risk of bias, imprecision, inconsistency, indirectness, and publication bias [22].

2.8. Statistical analyses

Data were recorded as total sample size and number of events (frequency) and were analyzed in STATA 17.0 statistical program (Stata Corp, College Station, TX, USA). Since considerable heterogeneity was expected among the included studies, it was decided to use a random effect model for the meta-analyses. Follow-up time varied between studies, and therefore, analyses were stratified based on follow-up time. The studies were divided into three groups: 30-day follow-up (follow-up between 10 and 30 days after discharge), 90-day follow-up (follow-up between 10 and 90 days), and one-year follow-up (follow-up between 10 days to 365 days).

Heterogeneity between the studies was assessed using I^2 statistics and the chi-square test. I^2 above 50% was defined as the presence of obvious heterogeneity. In cases of heterogeneity, the possible sources of heterogeneity were investigated using subgroup analysis. Since one-year follow-up after recovery included all 30-day and 90-day follow-up data, subgroup analysis was performed on one-year outcome after discharge. The country type was defined in two categories as developed and developing countries according to the World Bank definition; Developed countries were defined as countries with high-income economies while developing countries were defined as those with low- and middle-income economies [23].

Meta-regression was performed to investigate the relationship between the mean age of patients and the outcomes. For this purpose, the mean age of patients in each study was entered in the analyses as independent variables, and the hospital readmissions and post-discharge all-cause mortality were considered as dependent variables. Sensitivity analyses were performed according to the quality of the included studies and based on the country-level prevalence of hospital readmissions and post-discharge all-cause mortality. For this purpose, only studies on all COVID-19 patients were included and other settings were excluded. Finally, publication bias was investigated using Egger's test and funnel plots.

3. Results

3.1. Article screening process

The systematic search yielded 2531 studies, which included 1610 non-duplicated studies. In the manual search of gray literature and preprints, 18 potentially related papers were included. After reviewing the titles and abstracts of the articles, 157 peer-reviewed papers or preprinted manuscripts were reviewed and a total of 91 articles were entered into the present meta-analysis [8,14-18,24-108]. The reasons for excluding articles are shown in Fig. 1.

3.2. Summary of eligible studies

There were 28 prospective, 61 retrospective, and 2 ambidirectional cohorts. There were 32 studies on the USA population, 18 studies on the Chinese population, 13 studies on the Spanish population, and seven studies on the UK population. Also, three studies were conducted in Iran. These studies included 283,468 patients (51.19% male). The mean age of patients enrolled in the studies ranged from 36.7 to 88.5 years.

The setting of the patients in 76 studies were all COVID-19 patients regardless of the characteristics of included patients. Three studies were performed on the elderly population and two studies were performed on patients with cardiovascular disease. The population of other studies included patients with cirrhosis and liver injury, autoimmune diseases, cancer, fungal infections, human immunodeficiency virus (HIV), rheumatic and musculoskeletal disorders, acute kidney injury, non-severe COVID-19 patients, corticosteroids treated patients, and empiric antibiotics treated patients.

The COVID-19 diagnostic test was Reverse transcription-polymerase chain reaction (RT-PCR) in 63 studies, while 16 studies did not report the diagnostic test. The method of identifying COIVD-19 was mixed in 12 studies. In the mixed-method approach, the diagnostic method was RT-PCR or other diagnostic methods including imaging procedures, serological tests, or clinical symptoms. The discharge criteria were not reported in 69 studies. In 18 studies, discharge criteria included two consecutive negative RT-PCR and clinical improvement. Four studies had discharged patients only based on clinical improvement.

Follow-up time ranged from 10 to 365 days. 48 studies examined hospital readmissions, nine studies examined post-discharge all-cause mortality, and 34 studies examined both outcomes. Table 1 summarizes the characteristics of the studies.

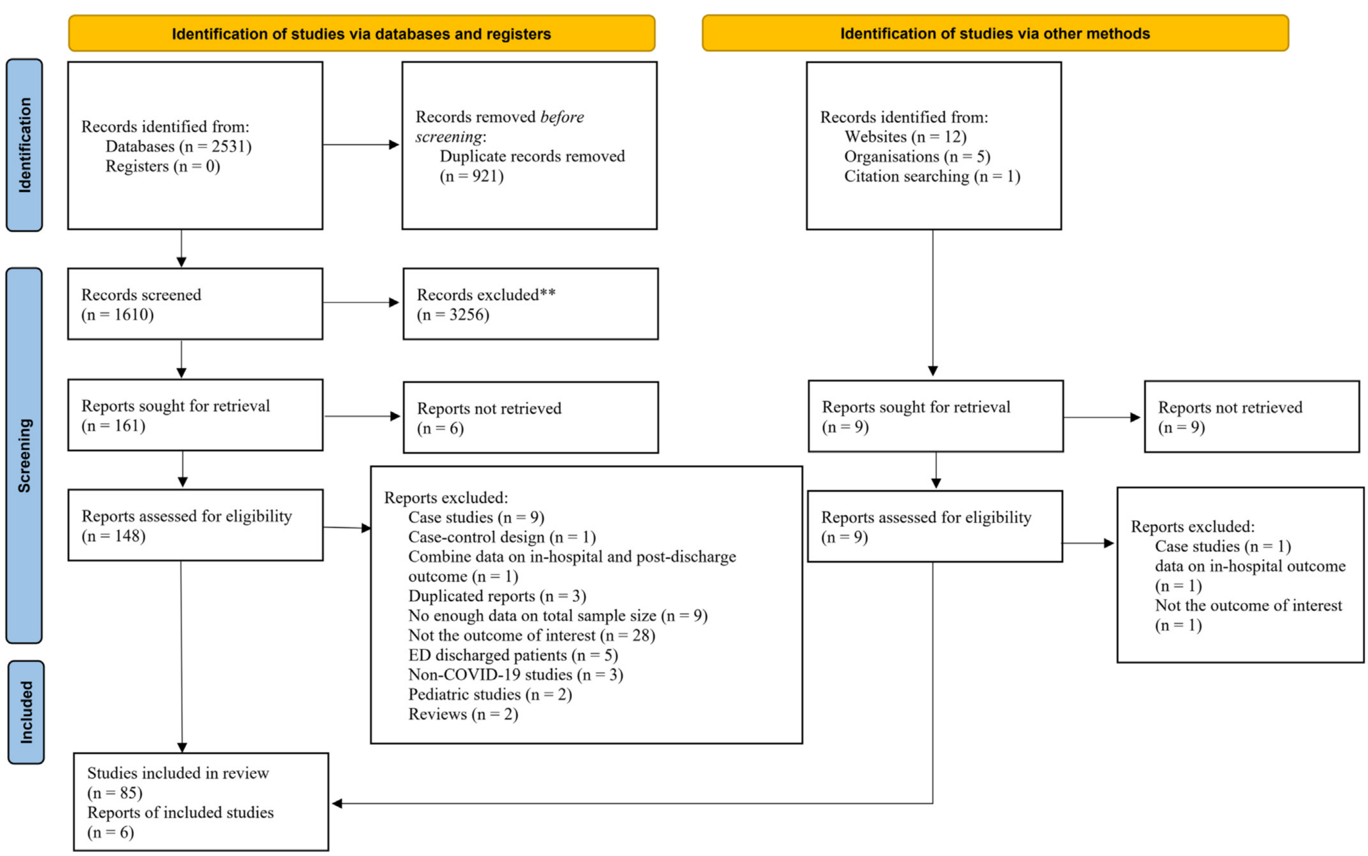

Fig. 1. PRISMA flow diagram for present studies.

Table 1
Summary characteristics of included studies.

Study	Study design	Setting of patients	COVID-19 diagnosis	Discharge criteria	Sample size	Male	Mean age (years)	FU (days)	Outcome
An, 2020; China [22]	PCS	All COVID-19 patients	RT-PCR	Two consecutive negative RT-PCR + clinical improvement	242	116	41.3	14	Readmission
Atalla, 2021; USA [15]	RCS	All COVID-19 patients	RT-PCR	Clinical improvement	279	191	61.3	30	Readmission
Ayoubkhani, 2021; UK [24]	RCS	All COVID-19 patients	NR	NR	47,780	26,279	65	253	Readmission, post-discharge mortality
Bajaj, 2021; USA [14]	PCS	All COVID-19 patients, cirrhosis and liver injury	NR	NR	122	46	60.6	90	Readmission, post-discharge mortality
Banerjee, 2021; USA [25]	PCS	All COVID-19 patients	RT-PCR	Stable patients with improving clinical trajectory	621	404	52.5	30	Readmission, post-discharge mortality
Barreto, 2021; Brazil [23]	RCS	All COVID-19 patients	RT-PCR or CT or IgM/IgG	NR	602	247	51.8	140	Readmission
Bowles, 2021; USA [26]	RCS	All COVID-19 patients	RT-PCR	NR	1409	718	67	180	Readmission, post-discharge mortality
Cao, 2020; China [27]	RCS	All COVID-19 patients	RT-PCR	NR	108	NR	NR	30	Readmission
Carrillo Garcia, 2021; Spain [28]	PCS	Elderly	RT-PCR or clinical or imaging or laboratory	NR	165	114	88.5	90	Readmission, post-discharge mortality
Chai, 2021; China [29]	PCS	All COVID-19 patients; cancer	RT-PCR	NR	588	328	64.7	365	Post-discharge mortality
Chaudhry, 2021; UK [30]	RCS	Corticosteroids treated patients	NR	NR	196	63	58.7	10	Readmission
Chen J, 2020; China [31]	RCS	All COVID-19 patients	RT-PCR	Two consecutive negative RT-PCR + clinical improvement	1087	452	60.2	52	Readmission
Chen SL, 2020; China [32]	RCS	All COVID-19 patients	RT-PCR	Two consecutive negative RT-PCR + clinical improvement	1282	628	44	28	Readmission
Choi, 2021; USA [33]	RCS	All COVID-19 patients	RT-PCR	NR	1008	NR	NR	30	Readmission
Chopra, 2020; USA [34]	RCS	All COVID-19 patients	NR	NR	1250	648	61.3	60	Post-discharge mortality
Connolly, 2021; Ireland [35]	PCS	All COVID-19 patients	NR	NR	502	179	40	12	Readmission
Divanoglou, 2021; Sweden [36]	AmbidiRCSectional	All COVID-19 patients	Laboratory assessment	NR	433	246	61.3	135	Post-discharge mortality
Donnelly, 2021; USA [37]	RCS	All COVID-19 patients	NR	NR	1775	1688	69.8	60	Readmission, post-discharge mortality
Frontera, 2021; USA [38]	PCS	All COVID-19 patients	RT-PCR	NR	380	248	67.5	180	Readmission, post-discharge mortality
Gabriel, 2021; Spain [39]	PCS	All COVID-19 patients	NR	NR	102	48	46.2	15	Readmission
García Abellán, 2021; Spain [40]	PCS	All COVID-19 patients	RT-PCR	NR	146	88	65	180	Readmission, post-discharge mortality
Gąsior, 2021; Poland [41]	RCS	MI and cardiovascular	NR	NR	2988	1352	69	180	Post-discharge mortality
Giannis, 2021; Greece [42]	PCS	All COVID-19 patients	NR	NR	4906	2633	61.7	92	Readmission, post-discharge mortality
Gordon, 2020; USA [43]	PCS	All COVID-19 patients	RT-PCR or clinical or imaging suspected	NR	1227	674	54	21	Readmission
Guarin, 2021; USA [44]	RCS	All COVID-19 patients	RT-PCR	NR	275	142	64.69	180	Readmission
Gudipati, 2020; USA [45]	RCS	All COVID-19 patients	NR	NR	266	125	61	30	Readmission
Gunster, 2021; Germany [46]	RCS	All COVID-19 patients	RT-PCR	NR	6518	4641	68.6	180	Readmission, post-discharge mortality
Gutiérrez, 2021; Spain [47]	RCS	All COVID-19 patients, autoimmune Diseases	RT-PCR	NR	13,940	7749	67.3	30	Readmission, post-discharge mortality
Gwin, 2021; USA [48]	RCS	All COVID-19 patients	RT-PCR	NR	151	88	59.6	30	Readmission

Table 1 (*continued*)

Study	Study design	Setting of patients	COVID-19 diagnosis	Discharge criteria	Sample size	Male	Mean age (years)	FU (days)	Outcome
Hasan, 2021; Bangladesh [17]	PCS	All COVID-19 patients	RT-PCR	NR	238	159	61.5	30	Readmission, post-discharge mortality
Herc, 2020; USA [49]	RCS	Fungal Infections	NR	NR	31	17	66	30	Readmission
Hernández-Biette, 2020; Spain [50]	PCS	Non-Severe COVID	RT-PCR	NR	74	35	54.6	14	Readmission, post-discharge mortality
Holloway, 2021; UK [51]	PCS	All COVID-19 patients	RT-PCR	NR	141	NR	NR	30	Readmission
Huang C, 2021; China [52]	ACS	All COVID-19 patients	RT-PCR	Two consecutive negative RT-PCR + clinical improvement	1733	897	56.3	199	Readmission, post-discharge mortality
Huang CW, 2021; USA [53]	RCS	All COVID-19 patients	RT-PCR	NR	2180	1238	54.7	30	Readmission, post-discharge mortality
Islam, 2021; UK [54]	RCS	All COVID-19 patients	RT-PCR	NR	403	211	66	60	Readmission, post-discharge mortality
Jain, 2020; USA [55]	PCS	All COVID-19 patients	NR	NR	18	10	65.3	90	Readmission
Jalilian Khave, 2021; Iran [56]	PCS	All COVID-19 patients	RT-PCR	NR	577	449	50.1	14	Readmission
Jeon, 2020; South Korea [57]	RCS	All COVID-19 patients	RT-PCR	Two consecutive negative RT-PCR + clinical improvement	7590	3095	47	180	Readmission
Kingery, 2021; USA [58]	RCS	All COVID-19 patients	RT-PCR	NR	1344	746	60.3	30	Readmission, post-discharge mortality
Kirkegaard, 2021; Spain [59]	RCS	All COVID-19 patients	RT-PCR	NR	629	318	60.28	60	Readmission, post-discharge mortality
Lavery, 2020; USA [60]	RCS	All COVID-19 patients	RT-PCR	NR	106,543	54,080	60	60	Readmission
Lee, 2020; USA [61]	RCS	HIV patients	RT-PCR	NR	72	44	61.3	30	Readmission
Leijte, 2020; Netherlands [62]	RCS	All COVID-19 patients	RT-PCR	NR	596	469	70	90	Readmission, post-discharge mortality
Leon, 2021; Spain [63]	PCS	Rheumatic and musculoskeletal	RT-PCR	NR	105	38	66.8	210	Readmission, post-discharge mortality
Li, 2020; China [64]	RCS	All COVID-19 patients	RT-PCR	Two consecutive negative RT-PCR + clinical improvement	85	55	48	60	Readmission
Luo, 2020; China [65]	RCS	All COVID-19 patients	RT-PCR	Two consecutive negative RT-PCR + clinical improvement	745	424	42.4	14	Readmission
Maestre-Muñiz, 2021; Spain [66]	RCS	All COVID-19 patients	RT-PCR	NR	266	201	71.5	365	Readmission, post-discharge mortality
Medler, 2020; USA [67]	RCS	All COVID-19 patients	RT-PCR	NR	337	NR	63.6	14	Readmission
Medranda, 2021; USA [68]	RCS	MI and cardiovascular	RT-PCR	NR	92	55	63.7	30, 90, 180	Readmission, post-discharge mortality
Meije, 2021; Spain [69]	PCS	All COVID-19 patients	RT-PCR	NR	323	171	68.8	45, 210	Readmission, post-discharge mortality
Menges, 2021; Switzerland [70]	PCS	All COVID-19 patients	RT-PCR	NR	81	43	59	180	Readmission
Mooney, 2021; UK [71]	RCS	Elderly	RT-PCR	NR	274	161	67	30	Readmission
Navvas, 2021; UK [72]	RCS	All COVID-19 patients	RT-PCR	NR	402	NR	NR	30	Post-discharge mortality
Nematshahi, 2021; Iran [73]	PCS	All COVID-19 patients	RT-PCR or imaging	NR	416	228	58.8	180	Readmission
Pan, 2021; China [16]	RCS	All COVID-19 patients	RT-PCR	Two consecutive negative RT-PCR + clinical improvement	1350	NR	NR	15	Readmission
Parra, 2020; Spain [74]	RCS	All COVID-19 patients	RT-PCR and imaging	NR	1368	872	64.4	21	Readmission
Pettit, 2021; USA [75]	RCS	Patients on empiric CABP antibiotics	RT-PCR	NR	246	116	60	30	Readmission
Pourhoseingholi, 2021; Iran [76]	RCS	All COVID-19 patients	CT scan	NR	1053	773	53	365	Readmission, post-discharge mortality

(continued on next page)

Table 1 (*continued*)

Study	Study design	Setting of patients	COVID-19 diagnosis	Discharge criteria	Sample size	Male	Mean age (years)	FU (days)	Outcome
Qiao,2020; China [77]	RCS	All COVID-19 patients	RT-PCR	Two consecutive negative RT-PCR + clinical improvement	15	8	36.7	30	Readmission
Quilliot, 2021; France [78]	PCS	All COVID-19 patients	RT-PCR or CT	NR	296	156	59.8	30	Readmission, post-discharge mortality
Ramos Martínez, 2021; Spain [79]	RCS	All COVID-19 patients	RT-PCR	NR	7137	4022	65.4	30	Readmission, post-discharge mortality
Reyes Gill, 2021; USA [80]	RCS	All COVID-19 patients	RT-PCR	NR	150	81	58.1	30	Readmission, post-discharge mortality
Richardson, 2020; USA [81]	PCS	All COVID-19 patients	RT-PCR	NR	2081	1162	63.3	10	Readmission
Rodriguez, 2021; USA [82]	PCS	All COVID-19 patients	RT-PCR	NR	3111	1250	60.9	30	Readmission
Roig-Marín, 2021; Spain [83]	RCS	Elderly	RT-PCR	NR	221	152	81.6	365	Post-discharge mortality
Romero-Duarte, 2021; Spain [84]	RCS	All COVID-19 patients	RT-PCR	NR	797	428	63	180	Readmission, post-discharge mortality
Saab, 2021; USA [85]	RCS	All COVID-19 patients	RT-PCR	NR	99	64	59.8	86	Readmission
Shallal, 2020; USA [86]	RCS	All COVID-19 patients	RT-PCR	NR	585	302	59.8	30	Readmission
Siddiqui, 2021; USA [87]	RCS	All COVID-19 patients; cirrhosis and liver injury	RT-PCR	NR	11,534	972	63.8	30	Readmission
Somani, 2020; USA [88]	RCS	All COVID-19 patients	RT-PCR	NR	2864	1663	65.7	14	Readmission
Spence, 2021; UK [89]	RCS	All COVID-19 patients	NR	NR	106	54	78.8	30, 60, 90	Readmission, post-discharge mortality
Spinicci, 2021; Italy [90]	RCS	All COVID-19 patients	NR	NR	107	59	67.3	56	Readmission, post-discharge mortality
Stockman, 2021; Germany [91]	RCS	AKI	NR	NR	37	NR	64.5	150	Post-discharge mortality
Suárez-Robles, 2020; France [92]	PCS	All COVID-19 patients	RT-PCR	NR	134	62	58.53	90	Readmission, post-discharge mortality
Tian, 2020; China [93]	PCS	All COVID-19 patients	RT-PCR	Two consecutive negative RT-PCR + clinical improvement	147	NR	NR	47	Readmission
Todt, 2021; Brazil [94]	RCS	All COVID-19 patients	RT-PCR	NR	251	150	53.6	90	Readmission, post-discharge mortality
Uyaroglu, 2021; Turkey [8]	RCS	All COVID-19 patients	RT-PCR or symptoms	Clinical improvement	154	77	44.5	30	Readmission
van den Borst,2021; Netherlands [95]	PCS	All COVID-19 patients	RT-PCR or symptoms	NR	98	74	59	90	Post-discharge mortality
Venturelli, 2021; Italy [96]	RCS	All COVID-19 patients	RT-PCR or IgM/IgG or symptoms	Two consecutive negative RT-PCR + clinical improvement	767	512	63	90	Post-discharge mortality
Verna, 2021; USA [97]	RCS	All COVID-19 patients	Laboratory assessment	NR	29,659	14,965	63.5	30	Readmission
Wang, 2020; China [98]	PCS	All COVID-19 patients	RT-PCR	Two consecutive negative RT-PCR + clinical improvement	94	59	49	30	Readmission
Weber, 2021; USA [18]	PCS	All COVID-19 patients	NR	NR	408	243	62.3	180	Readmission, post-discharge mortality
Wu, 2021; China [99]	RCS	All COVID-19 patients	RT-PCR	Two consecutive negative RT-PCR + clinical improvement	132	165	40.7	180	Readmission, post-discharge mortality
Yan, 2020; China [100]	RCS	All COVID-19 patients	RT-PCR	Two consecutive negative RT-PCR + clinical improvement	272	154	44.3	14	Readmission
Yang, 2020; China [101]	RCS	All COVID-19 patients	RT-PCR	Two consecutive negative RT-PCR + clinical improvement	479	224	42.8	90	Readmission
Ye S, 2021; USA [102]	RCS	All COVID-19 patients	RT-PCR	symptoms improvement	409	245	57.3	14	Readmission

Table 1 (*continued*)

Study	Study design	Setting of patients	COVID-19 diagnosis	Discharge criteria	Sample size	Male	Mean age (years)	FU (days)	Outcome
Ye X, 2021; China [103]	RCS	All COVID-19 patients	RT-PCR	Two consecutive negative RT-PCR + clinical improvement	141	73	45	30	Readmission
Yeo, 2021; USA [104]	RCS	All COVID-19 patients	RT-PCR	NR	1062	632	56.5	30	Readmission
Yuan, 2020; China [105]	RCS	All COVID-19 patients	RT-PCR	Two consecutive negative RT-PCR + clinical improvement	172	NR	NR	14	Readmission
Zheng, 2020; China [106]	RCS	All COVID-19 patients	RT-PCR	Two consecutive negative RT-PCR + clinical improvement	289	128	48.3	14	Readmission

COVID-19: Coronavirus disease 2019; CT: Computed tomography scan; FU: Follow up duration; NR: Not reported; PCS: Prospective cohort study; RCS: Retrospective cohort study; RT-PCR: Reverse transcriptase-polymerase chain reaction.

3.3. Hospital readmission rate of recovered COVID-19 patients after hospital discharge

82 studies examined hospital readmissions after patient recovery. These studies contained data from 266,677 patients. Analyses showed that the prevalence of one-year hospital readmissions was 10.34% (95% CI: 8.92, 11.77; 99.46%; $I^2 = 99.46\%$) (Fig. 2). Hospital readmissions during the first 30 and 90 days after discharge were 8.97% (95% CI: 7.44, 10.50; $I^2 = 99.04\%$) and 9.79% (95% CI: 8.37, 11.24; $I^2 = 99.33\%$), respectively (Supplementary Figs. 1 and 2). As can be seen, most hospital readmissions occur within the first 30 days.

Subgroup analysis on one-year follow-up showed that differences in country type and patient setting may be potential sources of heterogeneity since stratification of analyses according to these factors led to a decrease in heterogeneity. The hospital readmission rate was 10.68% in developed countries and 6.88% in developing countries. Also, the rate of hospital readmissions in elderly patients with COVID-19 (15.28%) and COVID-19 patients with underlying disease (19.63%) was higher than in other groups (Table 2).

3.4. Post-discharge all-cause mortality of COVID-19 patients

43 studies examined post-discharge all-cause mortality of COVID-19 patients. These studies contained data from 103,107 patients. Analyses showed that the prevalence of all-cause mortality during the one year after discharge was 7.51% (95% CI: 5.30, 9.72; 99.60%; $I^2 = 99.60\%$) (Fig. 3). All-cause mortality during the first 30 and 90 days were 7.87% (95% CI: 2.78, 12.96; $I^2 = 99.79\%$) and 7.63% (95% CI: 4.73, 10.53; $I^2 = 99.46\%$), respectively (Supplementary figs. 3 and 4). Most post-discharge deaths occur within the first 30 days.

Subgroup analysis showed that diversity in the characteristics of the patients may be a possible source of heterogeneity since stratification of the analyses based on the characteristics of patients led to a decrease in heterogeneity. The post-discharge all-cause mortality rate in COVID-19 patients with underlying disease (12.03%) was almost 100% higher than that of all COVID-19 patients regardless of underlying disease (6.59%) (Table 3).

3.5. Meta-regression

Meta-regression was performed to investigate the relationship between the mean age of patients and the outcomes. The findings showed that the mean age of COVID-19 patients at the time of admission was not related to the prevalence of hospital readmissions (meta-regression coefficient = 0.038; $p = 0.656$). However, the prevalence of post-discharge all-cause mortality increased with age (meta-regression coefficient = 0.360; $p = 0.009$) (Supplementary Fig. 5).

3.6. Sensitivity analysis

3.6.1. Quality of included studies

The risk of bias was high in 50 studies, some concern in four studies, and low in 37 papers (Supplementary Table 1). The prevalence of one-year hospital readmission in low-risk studies (high-quality studies) was 10.38% (Table 2), while the prevalence of 30-day hospital readmission in low-risk studies was 9.98%.

The prevalence of post-discharge all-cause mortality was 4.00% in low-risk studies (Table 3). Moreover, 30-day post-discharge all-cause mortality in low-risk studies was 3.24%.

3.6.2. Country-level differences of hospital readmissions and post-discharge mortality of COVID-19 patients

Sensitivity analysis showed that the highest prevalence of one-year hospital readmissions was observed in Germany (15.5%), Greece (15.5%), the UK (13.5%), Netherlands (11.7%), China (10.8%), USA (10.0%), and Sweden (9.9%). While the lowest hospital readmissions rate was seen in Brazil (5.4%), South Korea (4.3%), and France (4.1%).

The highest prevalence of one-year post-discharge all-cause mortality belonged to Italy (12.7%), the UK (11.8%), and Iran (9.2%). The lowest post-discharge all-cause mortality rates were observed in the Netherlands (3.8%), France (2.7%), Brazil (3.4%), Brazil (2.4%), Sweden (2.1%), China (1.2%), and Bangladesh (0.0%) (Fig. 4 and Table 4).

3.7. Publication bias and level of evidence

There was no evidence of publication bias regarding the hospital readmissions ($p = 0.473$) and post-discharge all-cause mortality ($p = 0.435$) assessments (Supplementary Fig. 6).

The overall level of evidence was very low in reporting the hospital readmissions and post-discharge all-cause mortality. According to the GRADE framework, the level of evidence for observational studies starts at low quality. A serious risk of bias and significant inconsistency was observed in the assessment of hospital readmission. Therefore, the quality of evidence was down-rated and reached very low. Also in the post-discharge all-cause mortality study, a high risk of bias and serious inconsistency was observed. Therefore, the certainty of the evidence was rated as very low (Supplementary Table 2).

4. Discussion

The present meta-analysis summarized the available pieces of evidence regarding hospital readmissions and post-discharge all-cause mortality in recovered COVID-19 patients. One-year follow-up showed that the prevalence of hospital readmissions and post-discharge all-cause mortality of recovered COVID-19 patients was 10.34% and 7.87%,

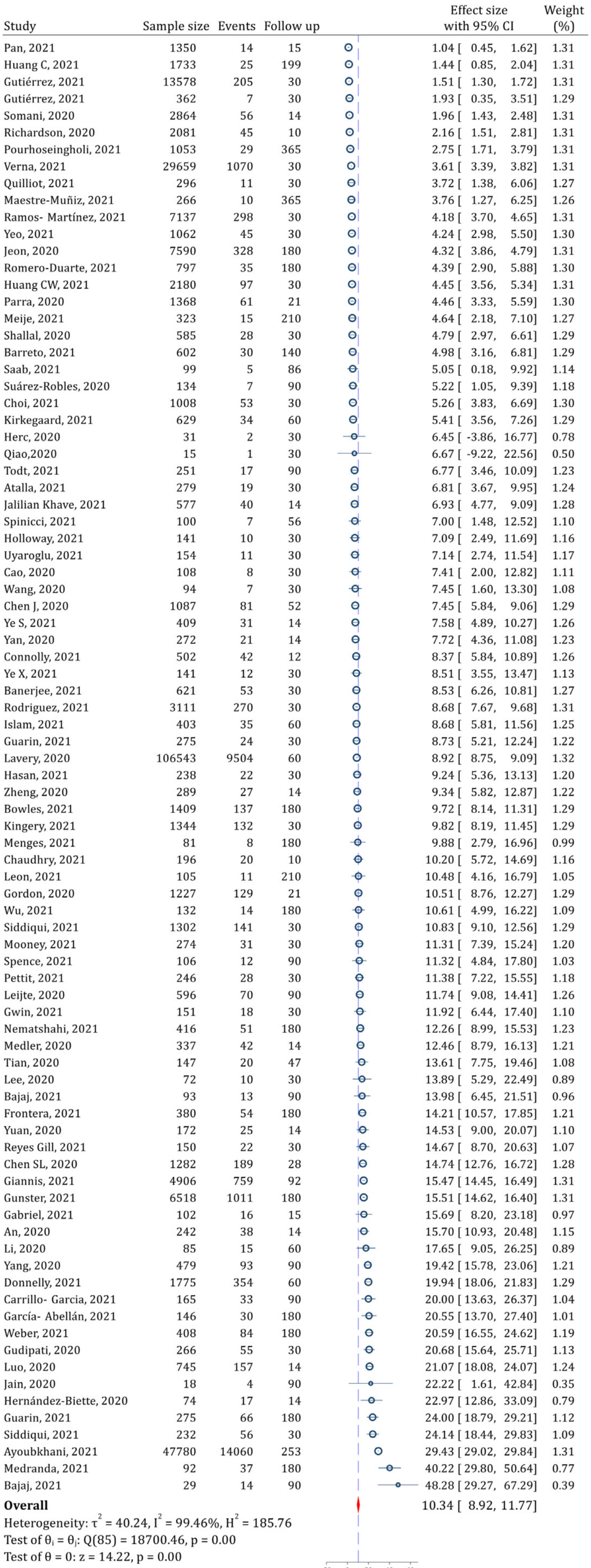

Fig. 2. Forest plot for prevalence of hospital readmission during one-year after recovery of COVID-19 patients. CI: Confidence interval.

respectively. Sensitivity analysis showed that the prevalence of hospital readmissions and post-discharge all-cause mortality in high-quality studies were 10.38% and 4.00%, respectively.

30-day hospital readmissions and post-discharge mortality were 8.97% and 7.87%, respectively. In addition, 30-day hospital readmissions and post-discharge mortality in high-quality studies were 9.98% and 3.24%, respectively. Therefore, most cases of hospital readmissions and mortality appear to occur within the first 30 days after discharge.

One of the interesting points in the present study was the higher hospital readmissions rate in developed countries compared to that of developing countries. The reason for this finding may be attributed to the higher medical benefits (better insurance coverage) provided in developed countries. Health insurance coverage in developing societies is much less widespread than in developed countries. In addition, access to medical services is limited in developing countries. Evidence shows that patients with poor insurance coverage account for a lower rate of readmissions. For example, Jeon et al. showed that the likelihood of readmission for COVID-19 patients with higher medical benefits is up to 5 times more than other patients [59]. Moreover, the data registries and follow-up of patients in developing countries in many instances do not exist, and in some other situations, patients' data loss is another obstacle. Therefore, the hospital readmissions rate may also be underestimated in developing countries.

A similar finding was observed for all-cause mortality. Post-discharge mortality was 7.78% in COVID-19 patients in developed countries and 3.84% in developing countries (Table 3). In addition to inaccurate tracking and recording of deaths in developing countries, the diversity of age distribution among communities should also be considered. The mean age of the population of developing countries is often lower than that of the population of developed countries, so this difference may be another reason for higher post-discharge all-cause mortality in developed countries compared to that of developing countries.

The relationship between age and increased post-discharge all-cause mortality of COVID-19 patients has been studied in some studies, the findings of which are sometimes contradictory. Some of these studies show a significant relationship between age and post-discharge all-cause mortality [39,48,60], while others do not report such a relationship [28,63]. The elderly population is heterogenous and suffers from various underlying diseases such as dementia, Parkinson's, and delirium, all of which affect the outcome of COVID-19 [109-111]. Therefore, differences between the populations included in these studies may be the cause of the contradictory findings. The present meta-analysis showed that age is a possible influencing factor on post-discharge all-cause mortality of COVID-19 patients. However, prospective studies need to be designed to examine the effect of age on mortality, alongside other confounders such as underlying disease.

The present study showed that the prevalence of hospital readmissions and post-discharge mortality is higher in COVID-19 patients with underlying diseases. This finding is somewhat in line with previous studies, showing that underlying diseases are possible risk factors of in-hospital outcomes of COVID-19 patients [112-116]. However, the number of studies examining risk factors for hospital readmissions and post-discharge mortality is small, and sometimes their quality is low due to various reasons. Drewett et al. (sample size = 169) showed that the presence of underlying disease is not associated with hospital readmissions [117]. While Joen et al., in their study of 7590 patients, showed that the risk of hospital readmissions increases to up to five times with increasing Charlson comorbidity index [18]. Also, Ramos-Martínez et al. showed that the presence of underlying respiratory diseases is a risk factor for hospital readmission, but there was no relationship between cardiovascular and kidney diseases and hospital readmissions [81]. Therefore, there seems to be a potential relationship

Table 2
Subgroup analysis for determination of source of heterogeneity in assessment of 1-years hospital readmission.

Variable	Number of analyses*	Prevalence (95% CI)	I2 (*p* value)
Country type			
Developed	79	10.68 (9.14, 12.22)	99.53 (<0.0001)
Developing	7	6.88 (4.52, 9.24)	85.48 (<0.0001)
Study design			
Prospective	27	11.52 (9.26, 13.79)	95.42 (<0.0001)
Retrospective	58	9.93 (8.15, 11.71)	99.63 (<0.0001)
Ambidirectional	1	1.44 (0.85, 2.04)	NA
Setting of patients			
All COVID-19 patients	77	9.71 (8.35, 11.06)	99.40 (<0.0001)
Elderly	2	15.28 (6.80, 23.76)	80.68 (0.023)
Presence of underlying disease or infection**	7	19.63 (7.41, 31.83)	96.22 (<0.0001)
COVID-19 diagnostic criteria			
RT-PCR	63	9.52 (8.04, 11.00)	99.26 (<0.0001)
Mixed criteria***	9	7.22 (4.02, 10.43)	98.14 (<0.0001)
NR	14	16.58 (12.24, 20.92)	97.89 (<0.0001)
Risk of bias score			
Low risk	36	10.38 (8.52, 12.24)	98.30 (<0.0001)
Some concern	3	17.16 (4.67, 38.98)	96.99 (<0.0001)
High risk	47	10.01 (7.99, 12.02)	99.64 (<0.0001)

NR: Not reported; CI: Confidence interval.
* Since some studies stratified their data according to different subgroups (such as according to underlying disease) the number of analyses is higher than number of studies.
** Underlying disease or infection included cirrhosis and liver injury, myocardial infarction, cardiovascular disease, autoimmune diseases, cancer, fungal infections, HIV infection, rheumatic and musculoskeletal and acute kidney injury.
*** Mixed criteria: RT-PCR or laboratory or clinical or imaging.

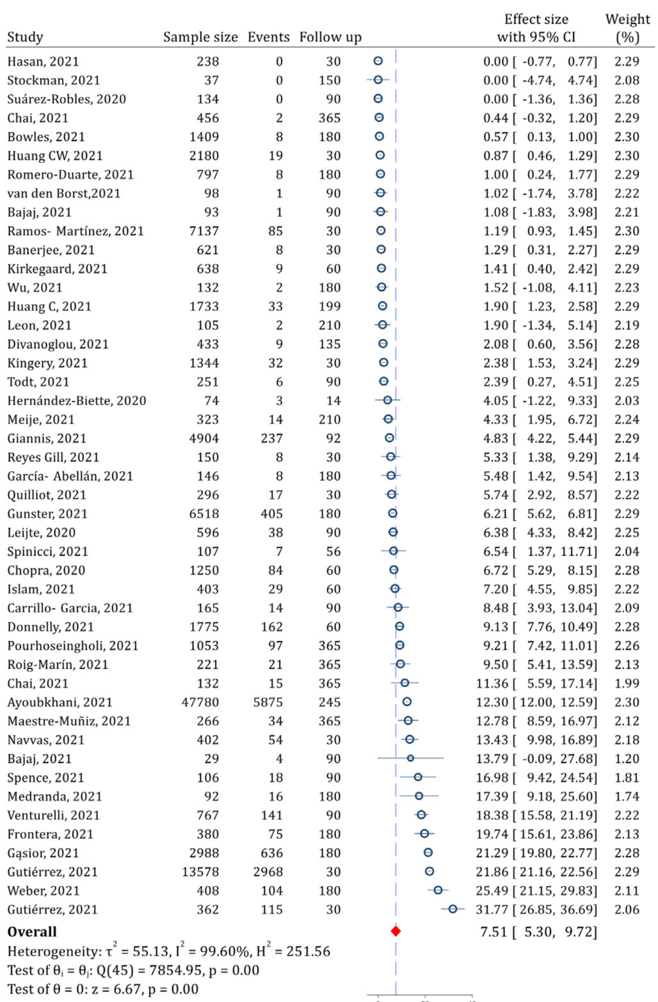

Fig. 3. Post-discharge all-cause mortality of COVID-19 patients during one-year after recovery. CI: Confidence interval.

between post-discharge of COVID-19 patients and underlying disease. But the current evidence is contradictory and comes from studies that have a low level of evidence and more research is needed in this field.

There were no eligibility criteria based on comorbidity in the current meta-analysis, and many hospitalized COVID-19 patients have at least one comorbidity [118,119]. Most of the included studies have been performed on a heterogeneous population of COVID-19 patients, from which some patients had a history of an underlying disease and others had no underlying diseases. On the other hand, many of comorbidities are exacerbated by COVID-19, such as cardiovascular diseases and coagulopathies [112-116,120]. In general, it seems that even in the presence of comorbidity COVID-19 is likely to be the main cause of readmission, because most of these readmissions occur within the first month after discharge.

Sensitivity analysis showed that hospital readmissions and post-discharge all-cause mortality varied across the countries. Part of this difference is related to socio-economic differences between countries. However, the included sample sizes are small in some countries. The included number of patients in the analysis of hospital readmissions and post-discharge all-cause mortality was less than 1000 patients in 8 (out of 16 countries) and 6 (out of 13 countries) countries, respectively. In other words, in almost half of the countries, the sample size included in the analysis was low, and therefore, care should be taken to interpret the findings regarding countries with low sample sizes.

HIV infection was reported as a risk factor for COVID-19 mortality in previous studies [121] and may cause a severe form of SARS-CoV-2 infection. In our meta-analysis, only one study assessed the post-COVID-19 readmission rate in HIV-infected patients. We performed a sensitivity analysis to assess the effect of this study on the findings. Excluding the HIV population from the analysis did not change the overall readmission rate of COVID-19 patients (10.34% vs 10.31%). Therefore, in the current study HIV infection was not a source of heterogeneity.

Another limitation of the present study was the lack of reporting patients' discharge criteria in the included studies. The standard criterion for discharge of COVID-19 patients is two consecutive negative RT-PCR, in addition to symptoms improvement [122], which was used only in 18 studies. However, in the remaining 73 studies, discharge criteria were not reported or relied only on symptoms improvement. A review

Table 3
Subgroup analysis for determination of source of heterogeneity in assessment of post-discharge all-cause mortality.

Variable	Number of analyses*	Prevalence (95% CI)	I2 (p value)
Country type			
Developed	43	7.78 (5.46, 10.11)	99.63 (<0.0001)
Developing	3	3.84 (−1.60, 9.27)	97.39 (<0.0001)
Study design			
Prospective	17	6.01 (2.58, 9.44)	98.76 (<0.0001)
Retrospective	27	8.84 (5.85, 11.84)	99.73 (<0.0001)
Ambidirectional	2	1.93 (1.32, 2.55)	0.00 (0.833)
Setting of patients			
All COVID-19 patients	37	6.59 (4.48, 8.74)	99.57 (<0.0001)
Elderly	2	9.05 (6.00, 12.09)	0.00 (0.754)
Presence of underlying disease or infection**	7	12.03 (3.03, 21.03)	97.86 (<0.0001)
COVID-19 diagnostic criteria			
RT-PCR	29	6.44 (3.68, 9.20)	99.64 (<0.0001)
Mixed criteria***	6	7.45 (2.39, 12.50)	96.33 (<0.0001)
NR	11	10.54 (5.62, 15.46)	99.43 (<0.0001)
Risk of bias score			
Low risk	19	4.00 (2.17, 5.83)	99.06 (<0.0001)
Some concern	2	9.17 (−5.98, 24.32)	91.54 (<0.0001)
High risk	25	10.00 (6.55, 13.46)	99.36 (<0.0001)

NR: Not reported; CI: Confidence interval.
* Since some studies stratified their data according to different subgroups (such as according to underlying disease) the number of analyses is higher than number of studies.
** Underlying disease or infection included cirrhosis and liver injury, myocardial infarction, cardiovascular disease, autoimmune diseases, cancer, fungal infections, HIV patients, rheumatic and musculoskeletal and acute kidney injury.
*** Mixed criteria: RT-PCR or laboratory or clinical or imaging.

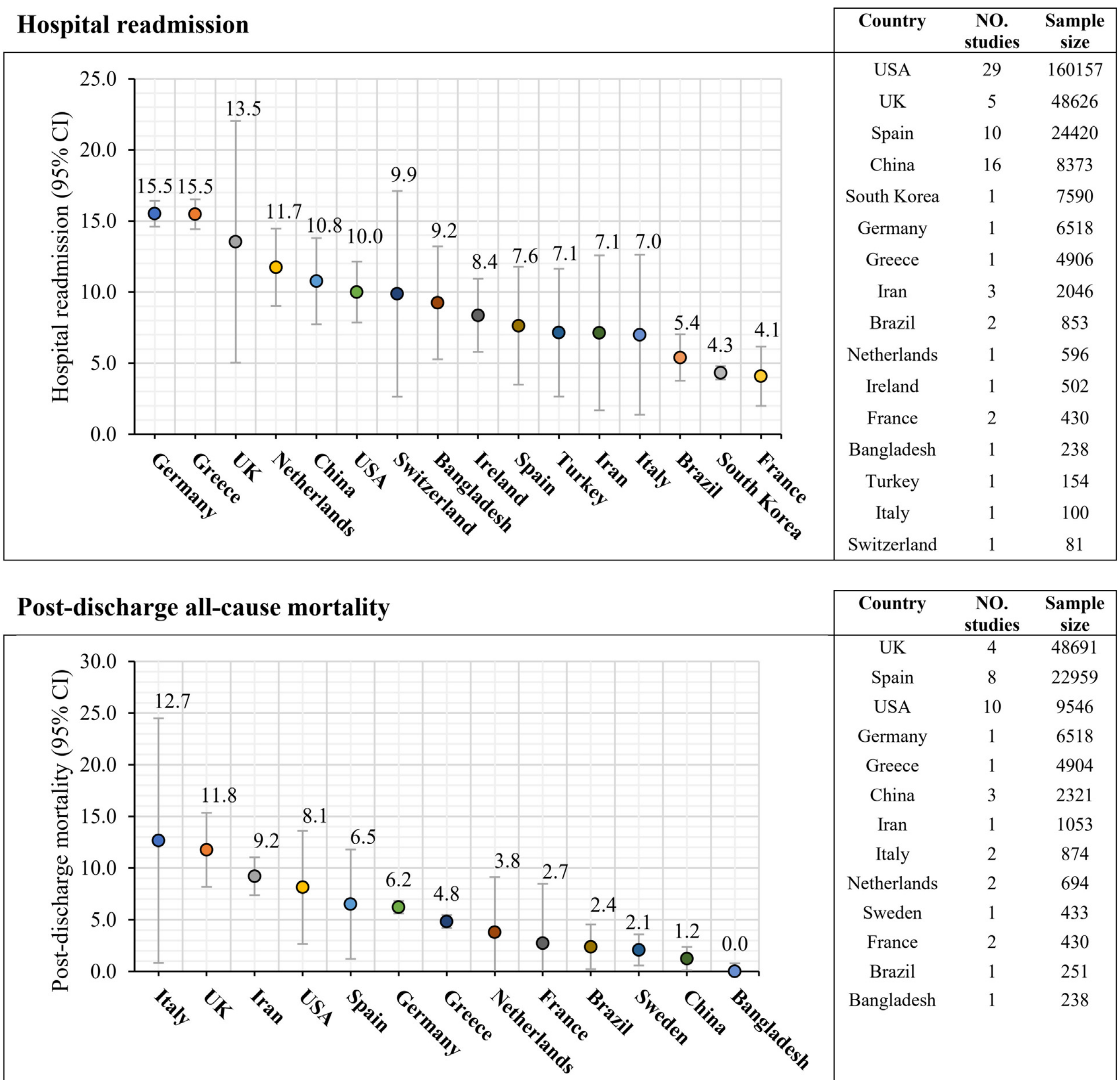

Fig. 4. Country-level hospital readmission and post-discharge mortality of COVID-19 patients.

Table 4
Country level hospital readmission and post-discharge mortality of COVID-19 patients

Country	Number of studies	Number of patients	Prevalence	95% confidence interval
Hospital readmission				
Germany	1	6518	15.5	14.6, 16.4
Greece	1	4906	15.5	14.4, 16.5
UK	5	48,626	13.5	5.2, 21.9
Netherlands	1	596	11.7	9.1, 14.4
China	16	8373	10.8	7.8, 13.7
USA	29	160,157	10.0	7.9, 12.1
Switzerland	1	81	9.9	2.8, 17.0
Bangladesh	1	238	9.2	5.4, 13.1
Ireland	1	502	8.4	5.8, 10.9
Spain	10	24,420	7.6	3.6, 11.7
Turkey	1	154	7.1	2.7, 11.5
Iran	3	2046	7.1	1.8, 12.5
Italy	1	100	7.0	1.5, 12.5
Brazil	2	853	5.4	3.8, 7.0
South Korea	1	7590	4.3	3.9, 4.8
France	2	430	4.1	2.0, 6.1
Post-discharge all-cause mortality				
Italy	2	874	12.7	1.1, 24.3
UK	4	48,691	11.8	8.3, 15.3
Iran	1	1053	9.2	7.4, 11.0
USA	10	9546	8.1	2.8, 13.5
Spain	8	22,959	6.5	1.3, 11.7
Germany	1	6518	6.2	5.6, 6.8
Greece	1	4904	4.8	4.2, 5.4
Netherlands	2	694	3.8	−1.5, 9.0
France	2	430	2.7	−2.9, 8.4
Brazil	1	251	2.4	0.3, 4.5
Sweden	1	433	2.1	0.6, 3.6
China	3	2321	1.2	0.1, 2.4
Bangladesh	1	238	0.0	−0.8, 0.8

study found that of the 10 countries with the highest prevalence of COVID-19, five did not have a discharge criterion, and in the other five countries there was considerable diversity in discharge criteria. This review strongly recommends defining uniform, standard and simple criteria for hospital discharge of COVID-19 patients [123]. During the COVID-19 pandemic and its outbreaks, the lack of hospital beds, medical facilities, and human resources caused patients to be discharged too early, leading to increased hospital readmissions and possible post-discharge deaths. Therefore, it is very important to define and standard discharge criteria in the treatment protocols of COVID-19 patients, to reduce the hospital readmission rates and deaths following the disease. Finally, it should be noted that the included studies were heterogeneous. Nevertheless, the possible sources of heterogeneity were found to be differences in population age, underlying diseases, and country type, the residual source of heterogeneity remained unclear.

5. Conclusion

Although the level of evidence was calculated to be very low, the current meta-analysis showed that 10.34% of recovered COVID-19 required hospital readmissions after discharge. Also, the one-year post-discharge all-cause mortality rate of COVID-19 patients is 7.87%. Most hospital readmissions and post-discharge all-cause mortality appear to occur within 30 days post-discharge. Therefore, in addition to adopting a standard criterion for discharge of COVID-19 patients, a 30-day follow-up program and patient tracking system for discharged COVID-19 patients seems necessary. Further prospective cohort studies are needed to explore the independent risk factors of hospital readmission and post-discharge mortality of COVID-19 patients.

Funding

None.

Author contribution

ZSR participated in designing, data gathering, analysis, and drafting of the paper.

Availability of data

All data used in the present study will be made available to qualified researchers on reasonable request.

Declaration of Competing Interest

There is no conflict of interest.

Acknowledgment

The author would like to thank Dr. Muhammed IM Gubari, for his invaluable contribution in collecting and summarizing the articles.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2021.10.059.

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