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RESEARCH ARTICLE

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Comparison of comorbidities among severe and non-severe COVID-19 patients in Asian versus non-Asian populations: A systematic review and meta-analysis

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Abstract

Objectives: This study aimed to evaluate the comorbidities among severe and non-severe COVID-19 patients in Asian versus non-Asian populations.

Design: Systemic review and Meta-analysis.

Methods: A systematic literature search was conducted using PubMed, Embase, Scopus and the web of science Database up to 24 March 2021. Odds ratios were calculated using a random-effects model.

Results: We identified 66 studies including 39 Asian and 27 non-Asian studies. This study demonstrated that the proportion of hypertension was significantly higher in severe group than in non-severe group for Asian (OR = 2.46) and non-Asian (OR = 1.60, 95% CI: 1.37–1.86, I^2 = 84%; $p < .00001$) patients. Similarly, the proportion of diabetes, cardiovascular disease and chronic kidney disease was significantly higher in severe group than in non-severe group for both Asian and non-Asian studies. We found no statistically significant difference between the severe versus non-severe group for cancer (OR = 1.26) and chronic obstructive pulmonary disease (OR = 1.32) among non-Asian patients.

KEYWORDS
comorbidity, COVID-19, meta-analysis, SARS-CoV-2, severe

1 | INTRODUCTION

The outbreak of Coronavirus disease (COVID-19), which was first reported in early December 2019 in Wuhan, China has emerged as one of the most serious global pandemic and global health hazard (Huang, Wang, et al., 2020). The cases of COVID-19 are still rapidly increasing with higher morbidity and mortality. Globally, there have been 146,067,511 confirmed COVID-19 patients by 25 April 2021 and among them 3,092,497 lost their lives (World Health Organization, 2021). The clinical manifestations highly range from asymptomatic to symptomatic and shows clusters of flu like symptoms such as fever, fatigue, myalgia, dry cough, dyspnoea, anorexia and so on (Hong et al., 2020; Huang, Wang, et al., 2020; Huang, Lian, et al., 2020). Patients are classified into four type, that is, mild, moderate, severe and critical based on clinical manifestation and laboratory findings. Some studies have documented that

Anju Puri and Lin He are contributed equally to this article.

COVID-19-infected patients who already have pre-existing comorbidities such as hypertension, diabetes, congestive heart failure, cardiovascular diseases, cerebrovascular disease, chronic kidney disease (CKD), chronic liver disease, cancer, chronic obstructive pulmonary disease and asthma leads to poor prognosis or even fatal outcomes (Giri et al., 2020; Gregoriano et al., 2020; Yang, Zheng, et al., 2020; Zhou, Yang, et al., 2020). In addition, the older people who already have above listed underlying chronic conditions are more susceptible to COVID-19. Severe cases admitted in intensive care unit with pre-existing comorbidities yield poorer clinical outcomes than those without (Abohamr et al., 2020; Guan et al., 2020; Huang, Wang, et al., 2020; Tabata et al., 2020).

Thus, it is critical to thoroughly understand and identify the actual high-risk comorbidities, which are closely associated with COVID-19 in order to do prompt management and prevent the deterioration from mild and moderate conditions to the severe ones. Thus far, most of published meta-analysis about the comorbidity in severe COVID-19 patients included limited studies and most studies included in these meta-analysis were conducted in China. Therefore, it is necessary to carry out a meta-analysis to give systematic evaluation of common comorbidities in severe and non-severe COVID-19 patients around the globe. To the best of our knowledge, this is the first study to compare comorbidities among severe and non-severe COVID-19 patients in Asian versus non-Asian populations.

2 | METHODS

2.1 | Eligibility criteria

For research article selection the inclusion criteria were as follows: (1) Study population: Studies with patients diagnosed with COVID-19; (2) Comparative studies: Studies that compared severe or ICU (elevated troponin T (TnT) level as the second choice if severe or ICU data were not given) and non-sever or non-ICU (normal TnT level as the second choice if non-severe or non-ICU data was not given) cases of COVID-19; and (3) The studies reporting parameters of comorbidities such as hypertension, diabetes, cardiovascular disease, cancer, chronic obstructive pulmonary disease and chronic kidney disease. Non-English studies, letters, case studies, editorials, conference abstract, vaccination trials studies and articles with only abstract were excluded. Studies with fewer than 20 cases were also excluded.

2.2 | Information sources and Searching strategies

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines (Moher et al., 2009). PRISMA checklist was followed step by step (Electronic Supplementary information Appendix S1). We used PubMed, Embase, Scopus and Web of Science online database to conduct a comprehensive search up to 24 March 2021, with following search terms: "COVID-19," "Novel coronavirus," "SARS-CoV-2," "Coronavirus disease-19," "Epidemiological character," "Clinical features," "Clinical character," "Clinical Presentation," "comorbidities," "Comorbidities" and "Complications." Full electronic search strategy in PubMed database can be found here (Electronic Supplementary information Appendix S2). We applied search filters to include English language studies. We screened reference lists of included studies to ensure literature saturation.

2.3 | Data extraction

Microsoft Excel database was used to record all available information. Two authors (AP and LH) who performed the literature search also independently extracted following items from each article: first author, publication year, country, study design, age, gender, sample size and number of people in severe and non-severe group. In case of missing data, we also contacted the authors of an article to obtain more precise data about the comorbidities of the patients evaluated. Disagreement occurred during research period were resolved by consensus with third author. The primary outcome measure was to compare the proportion of comorbidities such as hypertension, diabetes, cardiovascular disease, and chronic kidney disease in severe group versus non-severe group for both Asian and non-Asian studies.

2.4 | Risk of bias assessment

Methodological index for non-randomized studies (MINORS) (Slim et al., 2003) was used to assess methodological quality of included studies by two independent researchers. Each item in the MINORS has three scores: 0, unreported; 1, reported but inadequately or partially; and 2, adequately reported. The total score is 24. The detailed risk of bias for all the included studies using MINORS criteria score is presented in Table 1. According to MINORS criteria score the studies were classified as very low quality (0–6), low quality (7–12), moderate quality (13–18) and high quality (19–24). Two reviewers independently assessed the quality of included studies and disagreements were resolved through discussion with third reviewer. Publication bias among included studies was assessed by funnel plots and a symmetrical plot indicated low-risk publication bias.

2.5 | Statistical analysis

Meta-analysis was performed using RevMan software version 5.3. We calculated pooled odds ratio (OR) and 95% CI for comorbidities, in severe versus non-severe Asian and non-Asian studies. Heterogeneity between studies was assessed using the Cochran Q test and I^2 statistics. Generally, in cases of I^2 being larger than 50%, a random-effect model is used, otherwise a fixed-effect model is used. However, owing to the clinical heterogeneity inherent in

TABLE 1 MINORS rating scale for quality of included studies

Study	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩	⑪	⑫	Score
Asian studies													
Abohamr SI	2	2	2	2	2	0	1	0	2	2	2	2	19
Alqahtani AM	2	2	2	2	2	1	0	0	2	2	2	2	19
Bastug A	2	2	2	2	2	0	2	0	2	2	2	2	20
Cao J	2	2	2	2	2	1	0	0	2	2	2	2	19
Cao Z	2	2	2	2	2	0	1	0	2	2	2	2	19
Du RH	2	2	2	2	2	0	2	0	2	2	2	2	20
Guan WJ	2	2	2	2	2	0	0	0	2	2	2	2	18
Güner R	2	2	2	2	2	0	1	0	2	2	2	2	19
Guo T	2	2	2	2	2	0	0	0	2	2	2	2	18
Hong KS	2	2	2	2	2	0	1	0	2	2	2	2	19
Huang C	2	2	2	2	2	1	2	0	2	2	2	2	21
Huang R	2	2	2	2	2	1	1	0	2	2	2	2	20
Khamis F	2	2	2	2	2	0	2	0	2	2	2	2	20
Khan A	2	2	2	2	2	1	1	0	2	2	2	2	20
Lee JY	2	2	2	2	2	0	1	0	2	2	2	2	19
Lee SG	2	2	2	2	2	0	0	0	2	2	2	2	18
Li C	2	2	2	2	2	1	1	0	2	2	2	2	20
LI K	2	2	2	2	2	1	0	0	2	2	2	2	19
Li X	2	2	2	2	2	0	1	0	2	2	2	2	19
Lv Z	2	2	2	2	2	0	2	0	2	2	2	2	20
Omrani A	2	2	2	2	2	1	1	0	2	2	2	2	20
Shabrawishi M	2	2	2	2	2	0	1	0	2	2	2	2	19
Shahriarirad R	2	2	2	2	2	0	1	0	2	2	2	2	19
Shi S	2	2	2	2	2	1	2	0	2	2	2	2	21
Tabata S	2	2	2	2	2	0	0	0	2	2	2	2	18
Tian S	2	2	2	2	2	1	1	0	2	2	2	2	20
Wan S	2	2	2	2	2	1	1	0	2	2	2	2	20
Wang D	2	2	2	2	2	1	2	0	2	2	2	2	21
Wang W	2	2	2	2	2	0	2	0	2	2	2	2	20
Wang Y	2	2	2	2	2	1	0	0	2	2	2	2	19
Wang Z	2	2	2	2	2	1	2	0	2	2	2	2	21
Wei Y	2	2	2	2	2	1	1	0	2	2	2	2	20
Wu J	2	2	2	2	2	1	1	0	2	2	2	2	20
Xiong F	2	2	2	2	2	0	0	0	2	2	2	2	18
Xiong S	2	2	2	2	2	1	1	0	2	2	2	2	20
Yang L	2	2	2	2	2	0	0	0	2	2	2	2	18
Zhang G	2	2	2	2	2	0	1	0	2	2	2	2	19
Zhang JJ	2	2	2	2	2	0	0	0	2	2	2	2	18
Zhou J	2	2	2	2	2	0	0	0	2	2	2	2	18
Non-Asian studies													
Argenziano MG	2	2	2	2	2	1	2	0	2	2	2	2	21
Buckner FS	2	2	2	2	2	0	1	0	2	2	2	2	19
Cattelan AM	2	2	2	2	2	0	0	0	2	2	2	2	18
Ferguson J	2	2	2	2	2	1	1	0	2	2	2	2	20

(Continues)

TABLE 1 (Continued)

Study	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩	⑪	⑫	Score
Filardo TD	2	2	2	2	2	0	1	0	2	2	2	2	19
Garibaldi BT	2	2	2	2	2	0	0	0	2	2	2	2	18
Giustino G	2	2	2	2	2	1	1	0	2	2	2	2	20
Gregoriano C	2	2	2	2	2	1	0	0	2	2	2	2	19
Israelsen SB	2	2	2	2	2	0	0	0	2	2	2	2	18
Jourdes A	2	2	2	2	2	1	1	0	2	2	2	2	20
Kaeuffer C	2	2	2	2	2	0	0	0	2	2	2	2	18
Lombardi CM	2	2	2	2	2	0	1	0	2	2	2	2	19
Matangila JR	2	2	2	2	2	0	2	0	2	2	2	2	20
Ortiz-Brizuela E	2	2	2	2	2	0	0	0	2	2	2	2	18
Oud L	2	2	2	2	2	0	1	0	2	2	2	2	19
Pellaud C	2	2	2	2	2	1	1	0	2	2	2	2	20
Petrilli CM	2	2	2	2	2	0	0	0	2	2	2	2	18
Popov GT	2	2	2	2	2	0	0	0	2	2	2	2	18
Raad M	2	2	2	2	2	0	1	0	2	2	2	2	19
Reilev M	2	2	2	2	2	0	1	0	2	2	2	2	19
Samuels S	2	2	2	2	2	0	2	0	2	2	2	2	20
Schönfeld D	2	2	2	2	2	1	0	0	2	2	2	2	19
Stefan, G.	2	2	2	2	2	0	1	0	2	2	2	2	19
Sulejmani A	2	2	2	2	2	0	0	0	2	2	2	2	18
Suleyman G	2	2	2	2	2	0	1	0	2	2	2	2	19
Turcotte JJ	2	2	2	2	2	0	1	0	2	2	2	2	19
Yazdanpanah Y	2	2	2	2	2	1	1	0	2	2	2	2	20

Note: ① A clearly stated aim; ② Inclusion of consecutive patients; ③ Prospective collection of data; ④ Endpoints appropriate to the aim of the study; ⑤ Unbiased assessment of the study endpoint; ⑥ Follow-up period appropriate to the aim of the study; ⑦ Loss to follow up less than 5%; ⑧ Prospective calculation of the study size. ⑨ Appropriate selection of control group; ⑩ Synchronization of control group; ⑪ Baseline comparable between groups; ⑫ Appropriately statistical analysis. The global ideal score being 24 for comparative studies.

the data and the different effect sizes of included studies we used random-effects analysis for all meta-analyses. The I^2 values of <25%, 25%–50%, 50%–75% and 75%–100% were regarded as homogeneous, low, moderate and high heterogeneous levels, respectively. The *p*-value less than 0.05 was used to indicate statistical significance.

3 | RESULTS

Searches in electronic databases found 11,874 articles. After excluding duplicates (N = 7318), 4,556 citation records remained. Thereafter, 4,556 articles were screened in terms of title and abstract. 4,442 ineligible studies were excluded. The full text of 114 studies was assessed to determine their eligibility. We excluded 48 full texts, comprising 24 review articles, 15 non-comparative studies, five meta-analysis and four editorials. Ultimately, out of 114 full text article finally 66 articles, which met the inclusion criteria were included in the final analysis. Figure 1 shows a flow chart of studies selection process.

3.1 | Study characteristics and quality

A total of 66 studies were included among them 39 studies were Asian and 27 were non-Asian. Out of 39 Asian studies, most of them were carried out in China (N = 26) (Cao, Li, et al., 2020; Cao, Zheng, et al., 2020; Du et al., 2020; Guan et al., 2020; Guo et al., 2020; Huang, Wang, et al., 2020; Huang, Zhu, et al., 2020; Li, Jiang, et al., 2020; Li, Wu, et al., 2020; Li, Xu, et al., 2020; Lv et al., 2020; Shi et al., 2020; Tian et al., 2020; Wan et al., 2020; Wang, Hu, et al., 2020; Wang, Xin, et al., 2020; Wang, Yang, et al., 2020; Wang, Zhen, et al., 2020; Wei et al., 2020; Wu et al., 2020; Xiong, Liu, et al., 2020; Xiong, Tang, et al., 2020; Yang, Liu, et al., 2020; Zhang, Dong, et al., 2020; Zhang, Hu, et al., 2020; Zhou, Sun, et al., 2020), followed by Saudi Arabia (N = 4) (Abohamr et al., 2020; Alqahtani et al., 2020; Khan et al., 2020; Shabrawishi et al., 2020), South Korea (N = 3) (Hong et al., 2020; Lee, Hong, et al., 2020; Lee, Park, et al., 2020), Turkey (N = 2) (Bastug et al., 2020; Güner et al., 2020), Oman (N = 1) (Khamis et al., 2020), Qatar (N = 1) (Omrani et al., 2020), Iran (N = 1) (Shahriarirad et al., 2020), and Japan (N = 1) (Tab ata et al., 2020). Most of the non-Asian studies

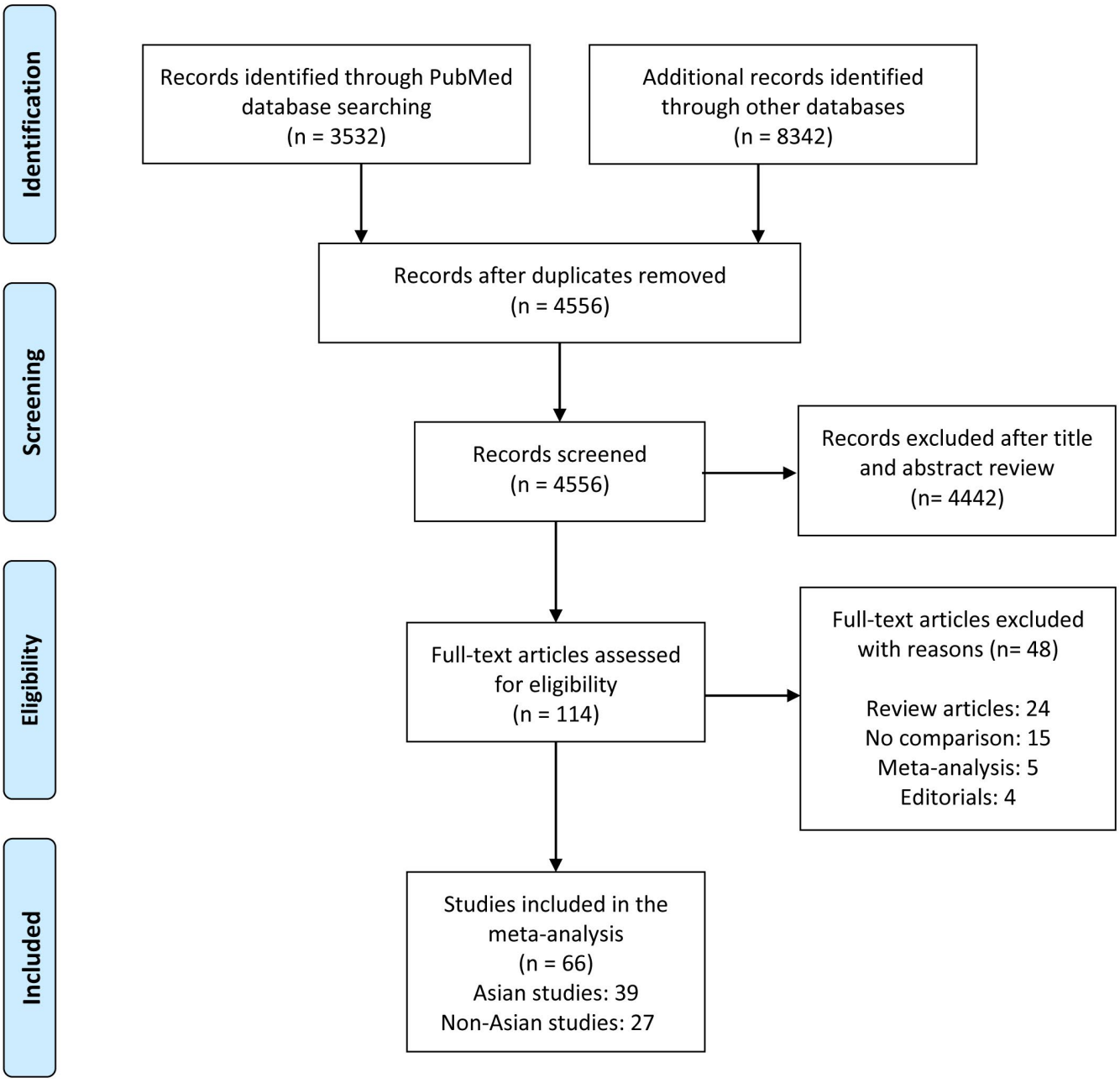

FIGURE 1 Flow diagram of study selection process

were conducted in United States (*N* = 12) (Argenziano et al., 2020; Buckner et al., 2020; Ferguson et al., 2020; Filardo et al., 2020; Garibaldi et al., 2021; Giustino et al., 2020; Oud & Garza, 2021; Petrilli et al., 2020; Raad et al., 2020; Samuels et al., 2021; Suleyman et al., 2020; Turcotte et al., 2020), followed by Italy (*N* = 3) (Cattelan et al., 2020; Lombardi et al., 2020; Sulejmani et al., 2021), France (*N* = 3) (Jourdes et al., 2020; Kaeuffer et al., 2020; Yazdanpanah, 2021), Switzerland (*N* = 2) (Gregoriano et al., 2020; Pellaud et al., 2020), Denmark (*N* = 2) (Israelsen et al., 2020; Reilev et al., 2020), Congo (*N* = 1) (Matangila et al., 2020), Mexico (*N* = 1) (Ortiz-Brizuela et al., 2020), Bulgaria (*N* = 1) (Popov et al., 2020), Argentina (*N* = 1) (Schönfeld et al., 2021) and Romania (*N* = 1) (Stefan et al., 2021). All included studies were published in 2020 and 2021 with varying sample size that ranged from 37 to 207,079 patients. The characteristics of the included studies are depicted in Table 2. We performed assessments of risk of bias for all the included studies using MINORS rating scale and reported in Table 1. The mean MINORS score was 19.23 ± 0.91 (range: 18–21) out of a possible 24 for comparative studies (Table 1). All of the included studies were moderate-to-high quality.

3.2 | Hypertension in Asian and non-Asian population

Fifty eight studies reported data on hypertension in severe and non-severe COVID-19 patients. The overall pooled incidence of

TABLE 2 Characteristics of the included studies

Study	Type of study design	Country	Total patients	Severe patients		Non-sever patients	
				Age, years[a]	Male	Age, years[a]	Male
Asian studies							
Abohamr SI	Retrospective	Saudi Arabia	768	47.4 ± 13.8	284	45.5 ± 13.5	305
Alqahtani AM	Retrospective	Saudi Arabia	458	NA	37	NA	361
Bastug A	Retrospective	Turkey	191	71 (28–91)	26	43 (18–83)	81
Cao J	Retrospective	China	244	62.20 ± 13.43	63	59.79 ± 13.49	44
Cao Z	Retrospective	China	80	71 ± 15	16	44 ± 16	22
Du RH	Retrospective	China	109	68.4 ± 9.7	36	72.7 ± 11.6	38
Guan WJ	Retrospective	China	1099	52 (40–65)	100	45 (34–57)	537
Güner R	Cohort	Turkey	222	62.2 ± 11.9	33	47.7 ± 16.1	99
Guo T	Retrospective	China	187	71.4 ± 9.43	34	53.53 ± 13.22	57
Hong KS	Retrospective	South Korea	98	63.2 ± 10.1	6	54.2 ± 17.7	32
Huang C	Prospective	China	41	49 (41–61)	11	49 (41–57.5)	19
Huang R	Retrospective	China	202	49 (35–59)	17	44 (33–53)	99
Khamis F	Retrospective	Oman	63	50 ± 17	21	47 ± 16	32
Khan A	Retrospective	Saudi Arabia	648	37 (27)	52	33 (18)	290
Lee JY	Retrospective	South Korea	694	NA	57	NA	155
Lee SG	Retrospective	South Korea	7339	66.8 ± 15.2	441	44.2 ± 17.8	2529
Li C	Retrospective	China	2068	69 (60–78)	282	61 (49–68)	723
LI K	Retrospective	China	83	53.7 ± 12.3	15	41.9 ± 10.6	29
Li X	Retrospective	China	548	65 (54–72)	153	56 (44–66)	126
Lv Z	Retrospective	China	354	62 (25–89)	77	61 (23–79)	58
Omrani AS	Retrospective	Qatar	5000	49.5 (39.5–60)	100	38 (30–49)	1067
Shabrawishi M	Retrospective	Saudi Arabia	150	49.8 ± 15.7	13	45.4 ± 16	58
Shahriarirad R	Retrospective	Iran	113	NA	7	NA	64
Shi S	Cohort	China	416	74 (34–95)	44	60 (21–90)	161
Tabata S	Retrospective	Japan	104	73 (55–77)	17	60 (40–71)	22
Tian S	Retrospective	China	262	61.4 (1–94)	26	44.5 (1–93)	101
Wan S	Retrospective	China	135	56 (52–73)	21	44 (33–49)	52
Wang D	Retrospective	China	138	66 (57–78)	22	51 (37–62)	53
Wang W	Retrospective	China	421	56 (45–63)	28	51 (38–60)	186
Wang Y	Retrospective	China	222	70 (65.5–80)	12	60.5 (48–67)	96
Wang Z	Retrospective	China	69	70.5 (62–77)	7	37 (32–51)	25
Wei Y	Retrospective	China	276	65 (60–72.8)	10	50 (39–57)	145
Wu J	Retrospective	China	280	63.04 ± 10.20	45	37.55 ± 17.10	106
Xiong F	Retrospective	China	131	63.3 ± 12.4	17	63.1 ± 13.4	58
Xiong S	Retrospective	China	116	64 (53–76)	38	56 (37–64)	42
Yang L	Retrospective	China	200	71 ± 13.4	16	52 ± 16.2	82
Zhang G	Retrospective	China	221	62 (52–74)	35	51 (36–64.3)	73
Zhang JJ	Retrospective	China	140	64 (25–87)	33	51.5 (26–78)	38
Zhou J	Retrospective	China	201	57 (46–66)	27	40 (31–53)	75
Non-Asian studies							
Argenziano MG	Retrospective	USA	1000	62 (52–72)	158	64 (51–77)	353
Buckner FS	Retrospective	USA	105	70 (23–97)	30	67 (25–96)	23
Cattelan AM	Retrospective	Italy	303	68 (56–77)	53	60 (47–72)	129

(Continues)

TABLE 2 (Continued)

Study	Type of study design	Country	Total patients	Severe patients		Non-sever patients	
				Age, years[a]	Male	Age, years[a]	Male
Ferguson J	Retrospective	USA	72	NA	NA	NA	NA
Filardo TD	Retrospective	USA	270	60 (51–68)	95	57 (48–67)	87
Garibaldi BT	Cohort	USA	832	58 (51–70)	96	60 (45–72)	266
Giustino G	Retrospective	USA	305	66 (56–74)	132	58 (47–70)	73
Gregoriano C	Retrospective	Switzerland	99	69 (57–75)	28	63.5 (56–76)	34
Israelsen SB	Retrospective	Denmark	175	68 (60–72)	16	73 (55–83)	69
Jourdes A	Cohort	France	263	67 (56–73)	33	64 (53–76)	122
Kaeuffer C	Prospective	France	1045	67.3 ± 13.4	303	65.6 ± 17.4	309
Lombardi CM	Retrospective	Italy	614	71.3 ± 12	201	64 ± 13.6	234
Matangila JR	Retrospective	Congo	160	58 (50–70)	31	51 (35–61)	41
Ortiz-Brizuela E	Prospective	Mexico	309	53 (40–64)	20	48 (29–60.5)	65
Oud L	Cohort	USA	136,728	NA	79,184	NA	2665
Pellaud C	Retrospective	Switzerland	196	65 (56–71)	30	74 (61–83)	89
Petrilli CM	Cohort	USA	2729	68 (58–78)	656	60 (48–71)	1016
Popov GT	Retrospective	Bulgaria	138	63 ± 12.8	33	48.3 ± 15.7	54
Raad M	Retrospective	USA	1020	70 (51–89)	229	59 (39–79)	280
Reilev M	Cohort	Denmark	11,122	68 (58–75)	228	72 (55–81)	984
Samuels S	Retrospective	USA	1692	65 ± 16.1	90	62 ± 19.1	166
Schönfeld D	Cohort	Argentina	207,079	66 (54–76)	3499	55 (37–72)	22,183
Stefan G	Cohort	Romania	37	67 (60–72)	5	62 (52–67)	14
Sulejmani A	Retrospective	Italy	175	74 (60–81)	90	61 (57–72)	15
Suleyman G	Retrospective	USA	463	63.8 ± 5.4	80	59.8 ± 15.2	85
Turcotte JJ	Retrospective	USA	117	70.2 ± 12.1	26	62.6 ± 16.9	36
Yazdanpanah Y	Cohort	France	246	68 (53–76)	51	60 (49–72)	88

[a]Age is presented as median (IQR) or mean ± *SD*.

hypertension was significantly higher in severe patients (50.90%) compared to non-severe patients (30.71%). In subgroup analysis, the proportion of hypertension was significantly higher in severe group than in non-severe group for Asian studies (OR = 2.46, 95% CI: 1.94–3.11; $p < .00001$) (Table 3 and Figure 2). There was high heterogeneity among the included studies ($I^2 = 82\%$). Similarly, non-Asian studies also showed statistically significant difference in hypertension incidence in severe and non-severe patients (OR = 1.60, 95% CI: 1.37–1.86, $I^2 = 84\%$; $p < .00001$) (Table 3 and Figure 2).

3.3 | Diabetes in Asian and non-Asian population

Data on the diabetes were reported in the 62studies. The overall pooled estimate showed significantly higher incidence of diabetes in severe patients than non-severe patients (OR = 1.95, 95% CI: 1.71–2.22, $I^2 = 83\%$; $p < .001$) (Table 3 and Figure 3). In Asian studies, the proportion of diabetes was statistically significant higher in severe patients compared with non-severe patients (OR = 2.70, 95% CI: 2.16–3.37, $I^2 = 71\%$; $p < .00001$). In non-Asian studies, the pooled odds of diabetes was also significantly higher in patients with severe disease than in those without (OR = 1.44, 95% CI: 1.27–1.63, $I^2 = 75\%$; $p < .00001$) (Table 3 and Figure 3).

3.4 | Cardiovascular disease in Asian and non-Asian population

Pooled findings of 48studies revealed significantly higher incidence of cardiovascular disease in severe patients compared to non-severe patients (OR = 2.47, 95% CI: 2.00–3.06, $I^2 = 79\%$; $p < .00001$) (Table 3 and Figure 4). The subgroup analysis of both Asian (OR = 3.72, 95% CI: 2.87–4.81, $I^2 = 62\%$; $p < .00001$) and non-Asian (OR = 1.52, 95% CI: 1.20–1.92, $I^2 = 71\%$; $p = .0005$) (Table 3 and Figure 4) studies demonstrated statistically significant differences in cardiovascular disease incidence between severe and non-severe patients.

3.5 | Cancer in Asian and non-Asian population

Data on cancer were reported by forty seven studies and pooled analysis revealed significantly higher incidence of cancer in severe

TABLE 3 Analysis of severe and non-severe patients of COVID-19 by using Mantel-Haenszel test

Variable	Number of studies	OR	95% CI	Severe	Non-severe	χ^{2a}	I^{2b}	Z^c	p
Overall studies									
Hypertension	58	2.01	1.75–2.32	6745	21,542	354.50	84	9.73	<.00001
Diabetes	62	1.95	1.71–2.22	51,816	12,662	367.68	83	9.95	<.00001
Cancer	47	1.63	1.29–2.06	15,467	3829	258.72	82	4.07	<.0001
COPD	39	2.04	1.60–2.61	1009	2996	104.82	64	5.77	<.00001
Cardiovascular disease	48	2.47	2.00–3.06	1477	2182	228.96	79	8.31	<.00001
Chronic kidney disease	38	2.23	1.77–2.81	35,985	3388	273.27	86	6.81	<.00001
Asian studies									
Hypertension	34	2.46	1.94–3.11	1425	2827	181.46	82	7.5	<.00001
Diabetes	36	2.70	2.16–3.37	1011	1802	121.19	71	8.70	<.00001
Cancer	29	2.31	1.68–3.18	162	275	39.27	29	5.17	<.00001
COPD	24	4.04	3.05–5.34	116	136	23.22	1	9.76	<.00001
Cardiovascular disease	29	3.72	2.87–4.81	563	790	73.33	62	9.97	<.00001
Chronic kidney disease	20	3.24	2.01–5.23	168	155	48.92	61	4.81	<.00001
Non-Asian studies									
Hypertension	24	1.60	1.37–1.86	5320	18,715	94.99	76	5.97	<.00001
Diabetes	26	1.44	1.27–1.63	50,805	10,860	98.98	75	5.75	<.00001
Cancer	18	1.26	0.96–1.64	15,305	3554	134.88	87	1.65	.10
COPD	15	1.32	1.02–1.70	893	2860	41.16	66	2.15	.03
Cardiovascular disease	19	1.52	1.20–1.92	914	1392	61.64	71	3.46	.0005
Chronic kidney disease	18	1.97	1.39–2.30	35,817	3233	172.20	90	4.52	<.00001

Abbreviations: 95% CI, 95% confidence interval; COPD, Chronic obstructive pulmonary disease; OR, odds ratio.

[a]Chi-squared test for heterogeneity.

[b]I^2 index to quantify the degree of heterogeneity.

[c]Z-statistics.

patients than non-severe patients (OR = 1.63, 95% CI: 1.29–2.06, $I^2 = 82\%$; $p < .0001$) (Table 3 and Figure 5). Furthermore, Asian studies showed statistically significant difference in cancer incidence between severe and non-severe patients (OR = 2.31, 95% CI: 1.68–3.18, $I^2 = 29\%$; $p < .00001$), while no statistically significant differences in cancer incidence were noted for non-Asian patients with COVID-19 (OR = 1.26, 95% CI: 0.96–1.64, $I^2 = 87\%$; $p = .10$) (Table 3 and Figure 5) in subgroup analysis.

3.6 | Chronic obstructive pulmonary disease (COPD) in Asian and non-Asian population

About the COPD thirty nine studies reported data in severe and non-severe COVID-19 patients. Pooled summary revealed significantly higher incidence of COPD in severe patients compared to non-severe patients (OR = 2.04, 95% CI: 1.60–2.6, $I^2 = 64\%$; $p < .00001$) (Table 3 and Figure 6). In subgroup analysis Asian studies showed statistically significant difference in COPD incidence between severe and non-severe patients (OR = 4.04, 95% CI: 3.05–5.34, $I^2 = 1\%$; $p < .00001$) (Table 3 and Figure 6). However, no statistically significant differences in COPD incidence were observed between severe versus non-severe for non-Asian patients (OR = 1.32, 95% CI: 1.02–1.70, $I^2 = 66\%$; $p = .03$).

3.7 | Chronic kidney disease in Asian and non-Asian population

In terms of chronic kidney disease, thirty eight studies reported data in severe and non-severe COVID-19 patients. Compared with non-severe, severe patients revealed significantly higher incidence of chronic kidney disease in pooled analysis (OR = 2.23, 95% CI: 1.77–2.8, $I^2 = 86\%$; $p < .00001$) (Table 3 and Figure 7). Additionally, there was statistically significant differences in both Asian (OR = 3.24, 95% CI: 2.01–5.23, $I^2 = 61\%$; $p < .00001$) and non-Asian (OR = 1.79, 95% CI: 1.39–2.30, $I^2 = 90\%$; $p < .00001$) (Table 3 and Figure 7) studies in terms of chronic kidney disease severity in subgroup analysis.

3.8 | Publication bias

Funnel plots for all six comorbidities are included in supplementary information (Figures S1–S6). Nearly symmetrical graphical funnel

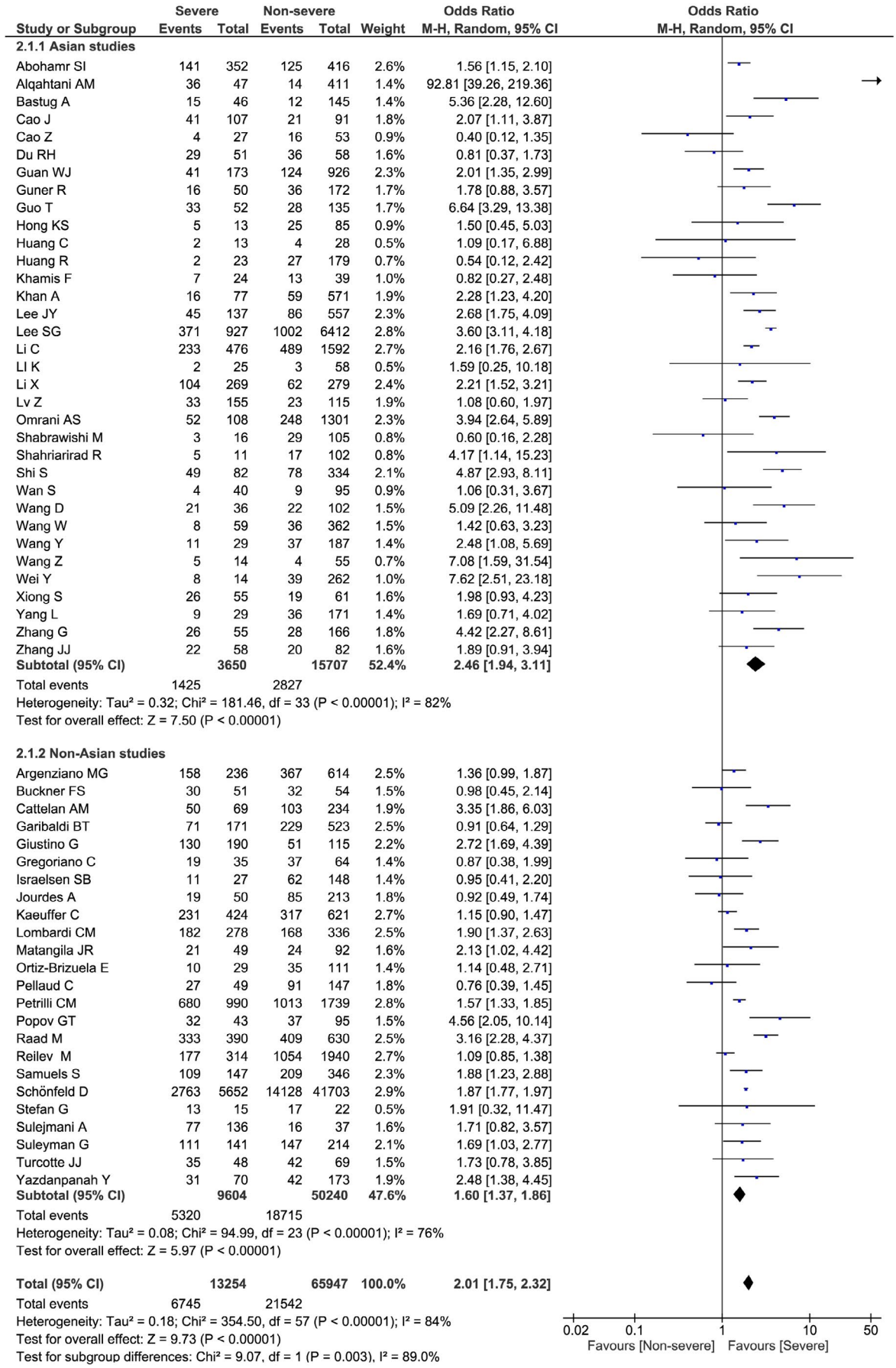

FIGURE 2 Forest plot for the ORs for comparing hypertension between severe and non-severe cases in SARS-CoV-2 infected Asian versus non-Asian patients

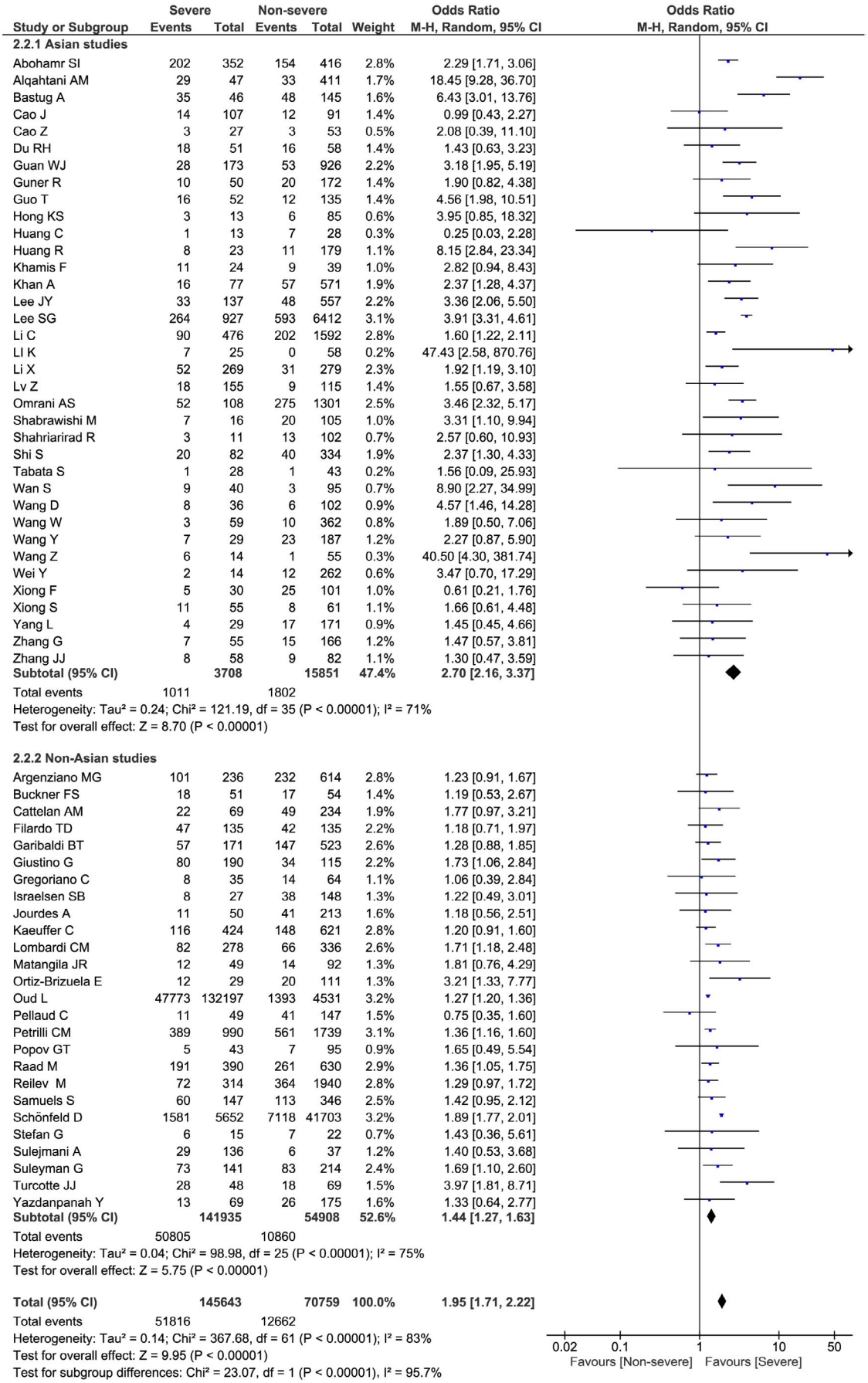

FIGURE 3 Forest plots depict the comparison of diabetes between severe and non-severe cases in SARS-CoV-2 infected Asian versus non-Asian patients

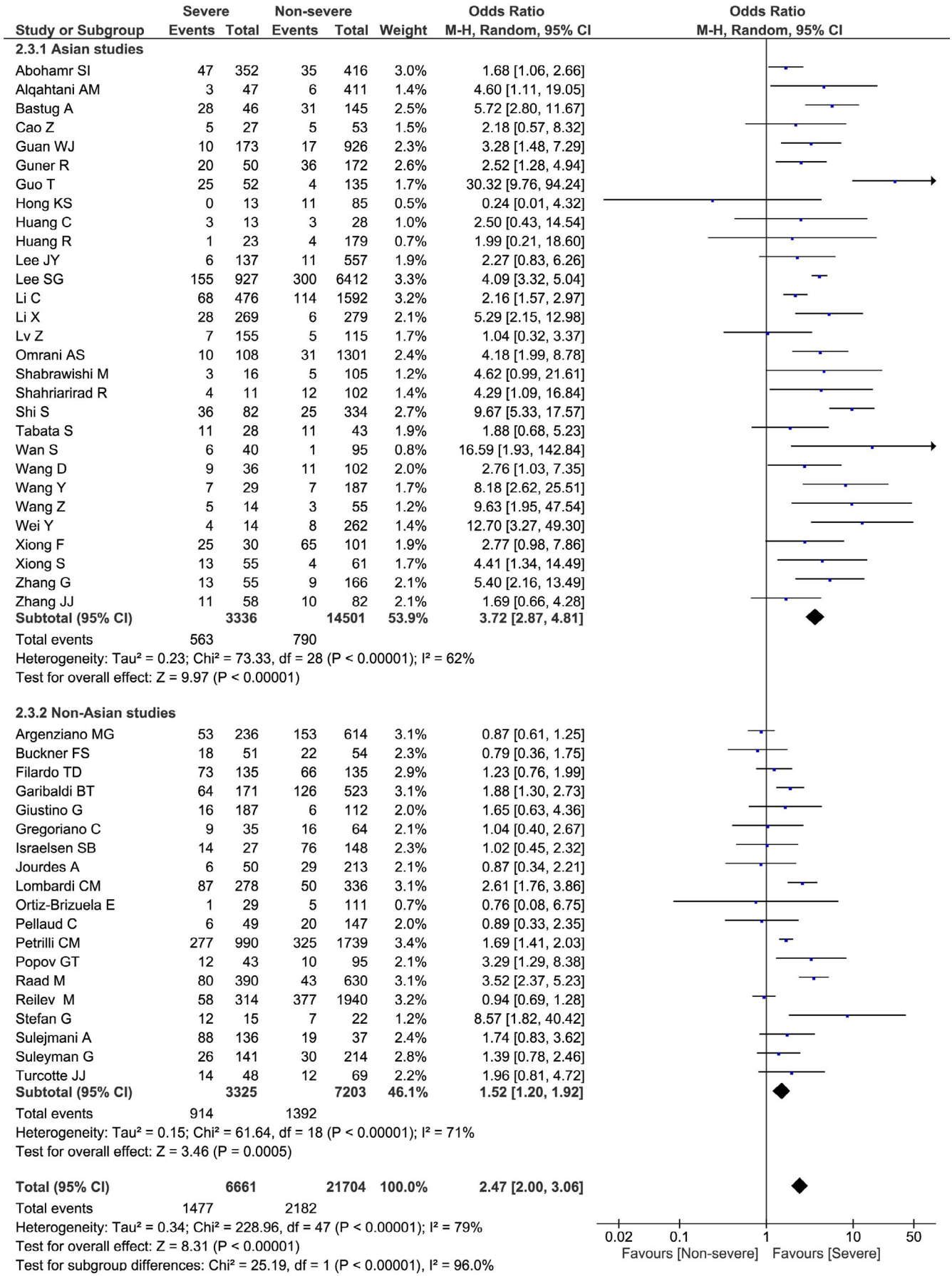

FIGURE 4 Forest plot for the ORs for comparing cardiovascular disease between severe and non-severe cases in SARS-CoV-2 infected Asian versus non-Asian patients

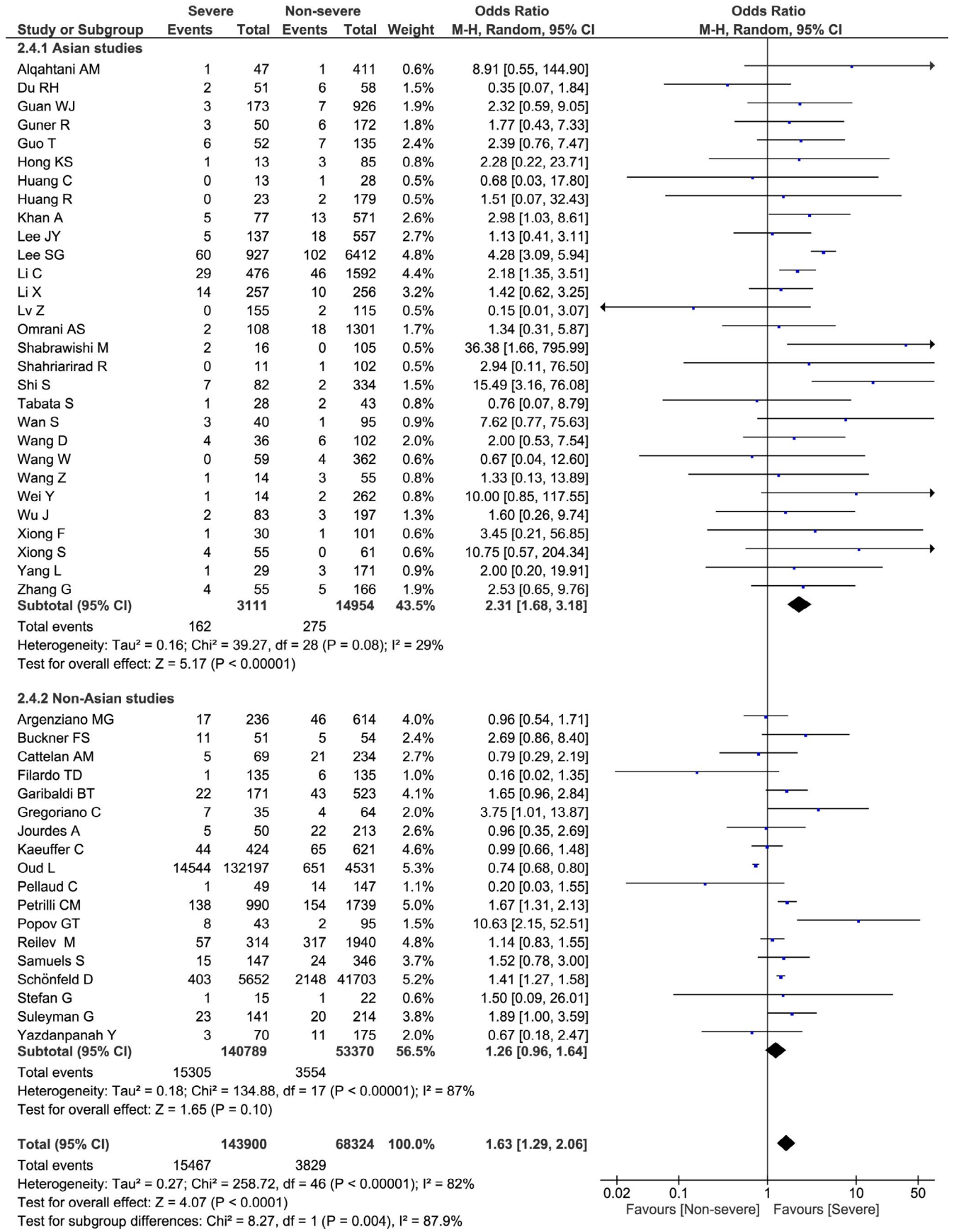

FIGURE 5 Forest plots depict the ORs for comparing cancer between severe and non-severe cases in SARS-CoV-2 infected Asian versus non-Asian patients

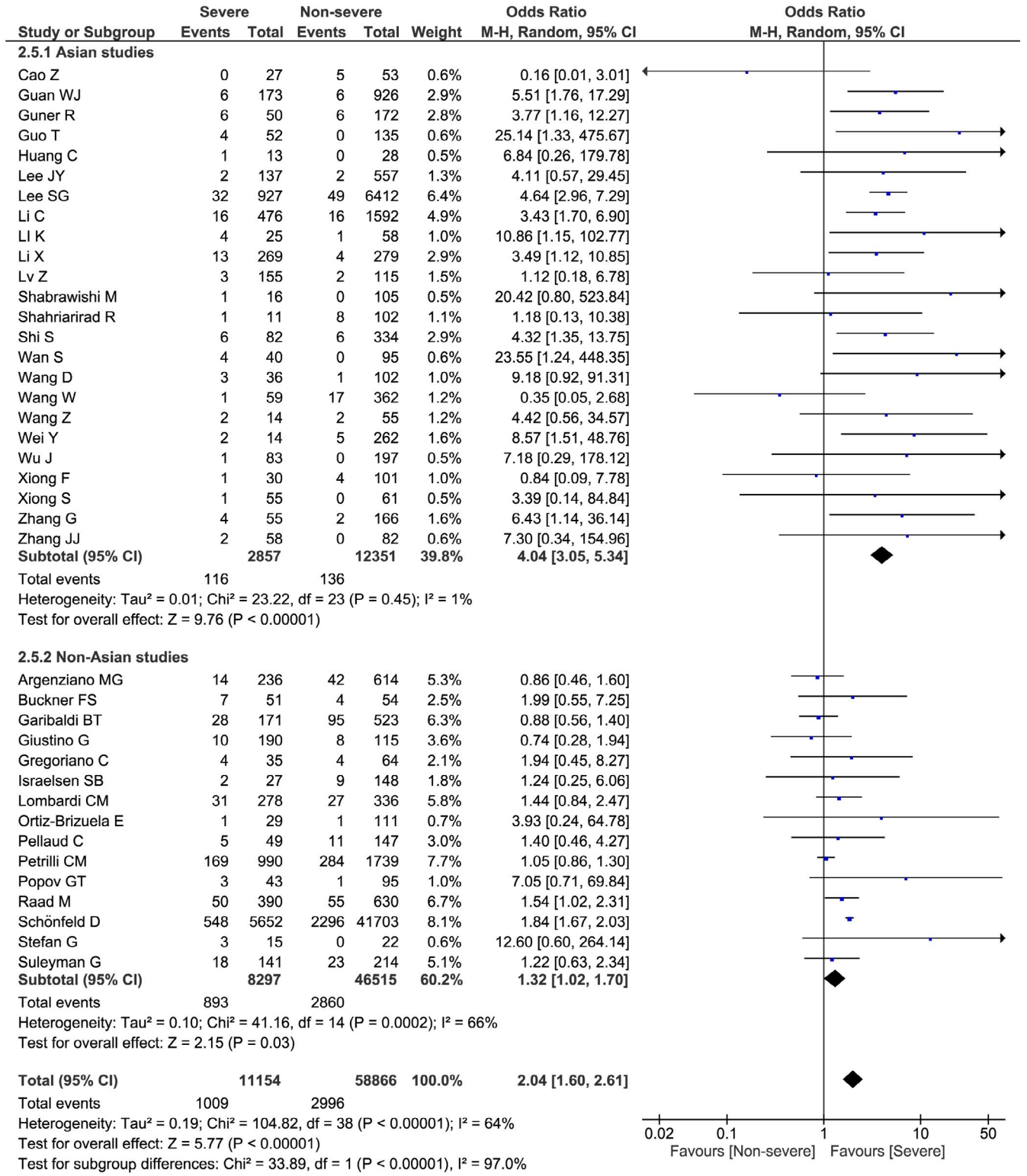

FIGURE 6 Forest plots depict the ORs for comparing COPD between severe and non-severe cases in SARS-CoV-2 infected Asian versus non-Asian patients

plots were obtained from all included studies evaluating comorbidities between severe and non-severe cases in SARS-CoV-2 infected Asian versus non-Asian patients. This visual symmetry and funnel shape suggested a low risk of publication bias.

4 | DISCUSSION

The rapid increase in the number of COVID-19 cases and death toll is having devastating social and economic consequences around

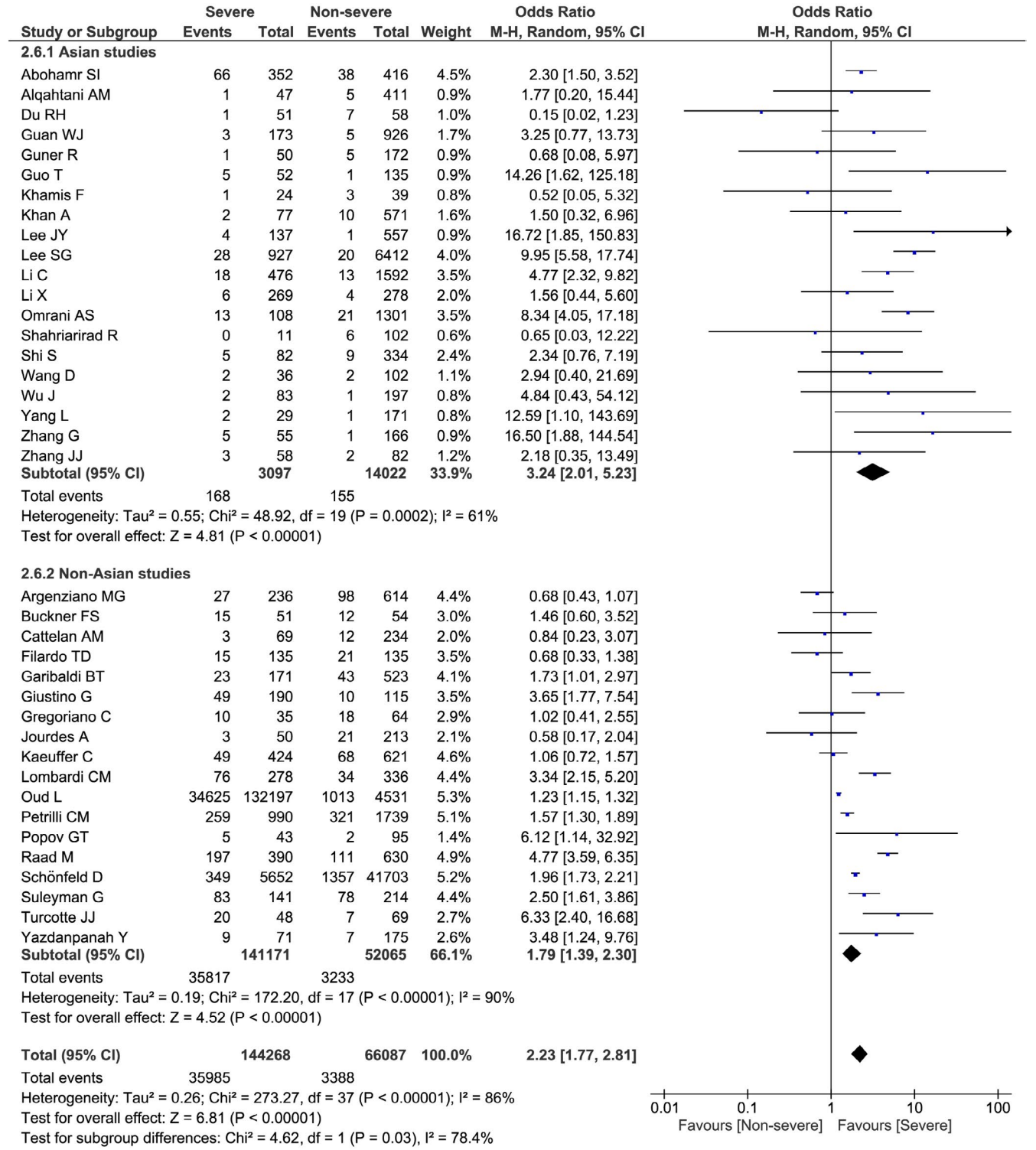

FIGURE 7 Forest plots depict the ORs for comparing chronic kidney disease between severe and non-severe cases in SARS-CoV-2 infected Asian versus non-Asian patients

the world. Early identification and timely treatment of severe cases are vitally important in resource-limited countries to save more lives with limited healthcare facilities. This systematic review and meta-analysis of comparative studies suggested that the severity of patients with COVID-19 was significantly associated with pre-existing comorbidities. To the best of our knowledge, this study is the first meta-analysis to compare the comorbidities between severe versus non-severe COVID-19 patients in Asian and non-Asian populations. We found that the incidence of hypertension, diabetes, cardiovascular disease and chronic kidney disease was significantly higher in severe compared to non-severe patients in both Asian and non-Asian group in terms of subgroup analysis.

Our findings are consistent with previous studies that showed a statistically significant association of pre-existing comorbidities with severe COVID-19 cases (Del Sole et al., 2020; Yang, Zheng, et al., 2020; Zhang, Lee, et al., 2020; Zhou, Yang, et al., 2020). Additionally, among Asian studies, there was a statistically significant difference between cancer and COPD incidence between severe and non-severe COVID-19 patients. However, the incidence of cancer and COPD in severe and non-severe non-Asian patients demonstrated no statistically significant difference.

Meta-analysis by Yin et al. (2021) assessed the role of comorbidity in COVID-19 progression in Chinese patients and indicated that chronic kidney disease, cardiovascular disease, cancer, diabetes and hypertension were the strongest risk factor in disease exacerbation. Besides, Yang, Zheng, et al. (2020) showed that the pooled odds ratio of hypertension, respiratory system disease and cardiovascular disease were 2.36, 2.46 and 3.42, respectively, between severe and non-severe patients. Another meta-analysis by Giri et al. (2020) concluded that incidence of hypertension, cardiovascular disease, diabetes and cancer in the severe group was statistically significant higher than non-severe group. However, in their meta-analysis, all included studies were from China. Although we could not find any meta-analysis that compared comorbidities between severe and non-severe COVID-19 patients for the non-Asian studies only; however, the result of individual studies published in non-Asian countries showed that hypertension, cardiovascular disease, diabetes and cancer incidences were higher in severe or ICU groups (Argenziano et al., 2020; Buckner et al., 2020; Cattelan et al., 2020; Ferguson et al., 2020; Filardo et al., 2020; Pellaud et al., 2020; Schönfeld et al., 2021). Our findings are in line with current knowledge that patients with comorbidities are more susceptible to severe infection.

Pre-existing cardiovascular disease and cardiovascular risk factors such as hypertension and diabetes enhance vulnerability to COVID-19 as the SARS-CoV-2 enters lung cells via the ACE2 receptor (Ni et al., 2020). Furthermore, COVID-19 may induce direct myocardial injury by upregulation of angiotensin-converting enzyme (Zheng et al., 2020). Additionally, renin–aldosterone–angiotensin system (RAAS) plays a vital role in the pathogenesis of COVID-19 and Tignanelli et al. (2020) revealed that hypertensive patients have hyperactive RAAS activation through angiotensin-2, which may lead to acute lung injury during SARS-CoV-2 virus infection. Previous studies (Al-Salameh et al., 2021; Zhou et al., 2021) have demonstrated that patients with diabetes were associated with significantly higher risk of suffering from severe COVID-19 confirming that inflammation is important in the pathogenesis of severe COVID-19. Due to weakened immune systems, people with cancer are considered as a highly vulnerable group for COVID-19. This was further supported by study by Liang et al. (2020) as people with cancer were at increased risk of severe clinical events in a nationwide cohort study in China. A recent meta-analysis that evaluated the effects of cancer on patients with COVID-19 also showed that people with cancer were more susceptible to COVID-19 especially for those who had lung cancer than those without lung cancer (Yang, Chai et al., 2021). A meta-analysis that was performed to evaluate the association of chronic kidney disease demonstrated that COVID-19 patients with pre-existing chronic kidney disease had significantly increased risks of progression to a severe condition and even death (Wang, Luo et al., 2021). Another study that examined the clinical courses of critically ill COVID-19 patients with and without pre-existing chronic kidney disease suggested that underlying kidney disease confers higher risk for individuals with COVID-19 with poorer COVID-19 outcomes (Flythe et al., 2021). Therefore, clinicians should closely monitor CKD patients with suspected COVID-19 to prevent disease progression. People with specific comorbid and underlying conditions are at high risk for COVID-19 severity and mortality. Hence, these population groups should be prioritized for access to COVID-19 vaccination regardless of their geographical location.

There are several limitations to this systematic review and meta-analysis. First, most of the studies included in the meta-analysis were retrospective and conducted in different countries, settings and variation in reporting of medical conditions may be present. Second, high heterogeneity among included studies might be due to the large variation among studies in the sample size. Third, there was heterogeneity in the definition of moderate and severe cases of COVID-19 patients, which might have contributed to the high heterogeneity of the meta-analysis. Fourth, as our topic was related to current pandemic and we already initiated literature searches hence we failed to register in the PROSPERO. However, during systematic processes involved in our literature review we strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines. Despite these limitations, to the best of our knowledge, our study is the first systematic review and meta-analysis that examined comorbidities among severe and non-severe COVID-19 patients by including a large number of high-quality studies from Asian and non-Asian countries with large sample sizes.

5 | CONCLUSION

In conclusion, this systemic review and meta-analysis showed that the incidence of hypertension, diabetes, cardiovascular disease and chronic kidney disease was significantly higher in severe compared to non-severe patients in both Asian and non-Asian population. Despite the continuous efforts to prevent and reduce severity of the disease the COVID-19 pandemic is exacting enormous medical and economic tolls on human life. Timely identification of comorbidities predictive for severe disease and ICU admission, can help frontline health workers such as doctors and nurses to effectively prioritize individual at risk in countries with limited resources. Patients with comorbidities have a tendency to develop severe or critical disease and have a poor disease outcome. More attention should be given to the care of patients with pre-existing comorbidities. More well designed and high-quality randomized-control studies that use standardized patient selection are needed to confirm our findings.

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Not applicable.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

AP, LH, MG and QHZ: conceptualization. AP, LH, MG and CFW: methodology. AP, LH, MG: statistical analysis. AP, LH, MG: data extraction and management. AP, LH, MG and QHZ: writing—original draft preparation. AP, LH, MG, QHZ and CFW: writing—review and editing. QHZ: supervision. All authors contributed to the article and approved the submitted version.

ETHICAL APPROVAL

Ethical review and approval is not required as this is systemic review and meta-analysis.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the studies included in this meta-analysis.

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SUPPORTING INFORMATION

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