Original Article

Clinical Determinants of Severe COVID-19 Disease – A Systematic Review and Meta-Analysis

Ankit Kumar Sahu, Roshan Mathew, Praveen Aggarwal, Jamshed Nayer, Sanjeev Bhoi, Swayamjeet Satapathy[1], Meera Ekka

Department of Emergency Medicine, All India Institute of Medical Sciences, New Delhi, [1]Department of Nuclear Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Abstract

Background: A systematic review and meta-analysis of available studies was performed to investigate the clinical characteristics that can predict COVID-19 disease severity. **Materials and Methods:** Databases including PubMed, Embase, and Web of Science were searched from December 31, 2019, to May 24, 2020. Random-effects meta-analysis was used for summarizing the Pooled odds ratio (pOR) of individual clinical characteristics to describe their association with severe COVID-19 disease. **Results:** A total of 3895 articles were identified, and finally, 22 studies comprising 4380 patients were included. Severe disease was more common in males than females (pOR: 1.36, 95% confidence interval [CI]: 1.08–1.70). Clinical features that were associated with significantly higher odds of severe disease were abdominal pain (pOR: 6.58, 95% CI: 1.56–27.67), breathlessness (pOR: 3.94, 95% CI: 2.55–6.07), and hemoptysis (pOR: 3.35, 95% CI: 1.05–10.74). pOR was highest for chronic obstructive pulmonary disease (pOR: 2.92, 95% CI: 1.70–5.02), followed by obesity (pOR: 2.84, 95% CI: 1.19–6.77), malignancy (pOR: 2.38, 95% CI: 1.25–4.52), diabetes (pOR: 2.29, 95% CI: 1.56–3.39), hypertension (pOR: 1.72, 95% CI: 1.23–2.42), cardiovascular disease (pOR: 1.61, 95% CI: 1.31–1.98) and chronic kidney disease (pOR: 1.46, 95% CI: 1.06–2.02), for predicting severe COVID-19. **Conclusion:** Our analysis describes the association of specific symptoms and comorbidities with severe COVID-19 disease. Knowledge of these clinical determinants will assist the clinicians in the risk-stratification of these patients for better triage and clinical management.

Keywords: Clinical determinants, clinical predictors, COVID-19, meta-analysis, severe disease

Introduction

The novel coronavirus, named as severe acute respiratory syndrome coronavirus 2, was identified in Wuhan, China, in December 2019. The disease caused by the virus, COVID-19, has created havoc all over the world and has been declared pandemic by the World Health Organization (WHO). As of March 21, 2020, 11,183 patients have succumbed to this disease and with the rapid spread of the disease, these numbers might run into millions.[1]

The clinical spectrum of COVID-19 disease is wide, ranging from nonsevere (asymptomatic infection and mild respiratory tract infection) to severe disease (severe pneumonia and critical illness, including multiorgan dysfunction).[2] In a case series of 44,672 confirmed COVID-19 patients, 14% had severe, and 5% had critical disease.[2] However, most of the patients present with fever, dry cough, myalgia and have a favorable prognosis.[2] Older patients and those with comorbidities progress to severe disease and have worse outcomes.[3]

Access this article online

Quick Response Code:

Website: www.jgid.org

DOI: 10.4103/jgid.jgid_136_20

With overwhelmed health-care systems and no proven treatment, it is important to identify the patients who could have a high likelihood of progression to severe disease. This will help the concerned physicians to allocate the resources judiciously. The goal of this investigation was to identify the clinical determinants which are associated with severe COVID-19 disease.

Materials and Methods

Data sources and searches

This systematic review was performed according to the Preferred Reporting Items for Systematic Review and

Address for correspondence: Dr. Jamshed Nayer, Department of Emergency Medicine, All India Institute of Medical Sciences, New Delhi, India.
E-mail: jamshednayer@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Sahu AK, Mathew R, Aggarwal P, Nayer J, Bhoi S, Satapathy S, *et al*. Clinical determinants of severe COVID-19 disease – A systematic review and meta-analysis. J Global Infect Dis 2021;13:13-9.

Received: 12 June 2020 **Revised:** 06 August 2020
Accepted: 24 August 2020 **Published:** 29 January 2021

Meta-analysis (PRISMA). Databases including PubMed, Embase, and Web of Science were searched from December 31, 2019, to May 24, 2020. There were no restrictions in terms of country, publication language or publication date. Reference lists of all relevant articles and "related citation" search tool of PubMed were checked for any additional publications. The detailed search criteria used are available in Supplement.

Selection criteria

Study selection was performed by two independent investigators (A. S. and P. A.). We included studies that focused on individual symptoms and comorbidities of laboratory-confirmed COVID-19 patients and reported the data according to disease severity or ICU admission. Case reports, duplicate publications, reviews, editorials, letters, and family-based studies, studies with insufficient data on symptoms/comorbidities on admission in either severe or non-severe disease groups, and studies reporting exclusively on pediatric (<18 years age) or pregnant populations were excluded. Discrepancies between the reviewers were resolved in the presence of a third reviewer (J. N.).

Data abstraction and quality assessment

Data collected included: study characteristics – authors, publication date, study design, country, sample size; patient's characteristics – median age with interquartile range, sex (% men); criteria for severe disease; total number of severe and non-severe patients; and clinical characteristics (clinical features and comorbidities) at admission – overall prevalence and prevalence among severe and non-severe patients. One reviewer extracted the data (A. S.) and second reviewer (S. S) verified the data independently. The methodological quality of the study was assessed with the Appraisal tool for Cross-Sectional Studies (AXIS) tool.[4] Two authors (S. S, A. S.) performed the quality assessment separately, and disagreements were resolved by consensus in the presence of a third reviewer (P. A.). In the AXIS tool, for every correct answer, score of one was assigned to each of the twenty questions.

Quantitative data synthesis

Patient numbers were extracted across all the included studies for each group (severe and non-severe) according to the individual symptoms and comorbidities. The odds ratio (OR, 95% confidence intervals [CIs]) of individual clinical characteristics was used to describe their association with severe COVID-19 disease. These ORs were further pooled using random-effects meta-analysis. To assess the heterogeneity among studies, inconsistency statistics (I^2) were calculated. I^2 >50% was considered as significant heterogeneity. Publication bias was visually analyzed from Funnel plots and Egger's regression was also performed. P value for Egger's regression coefficient < 0.05 was considered as significant publication bias. All data were collected in Microsoft Excel Spreadsheet (MS Office – 2018). Random-effects analysis, generation of forest plot, assessment of heterogeneity, and publication bias were performed with the METAN platform for STATA (version-14.2); StataCorp, College Station, TX.

As the study design was a systematic review and meta-analysis, Institute Ethics Committee approval was not sought.

Results

Search results and study characteristics

The literature search flow diagram is summarized in PRISMA format [Figure 1]. Using our search criteria (available in supplement), we identified 3895 studies, of which 3645 were from PubMed, 50 were from EMBASE, and 200 were from Web of Science. A total of 209 records were screened after the removal of duplicates. A total of 87 full-text articles were assessed for eligibility and 65 articles were excluded due to various reasons, as shown in Figure 1. Finally, 22 studies were included in this meta-analysis.

Characteristics of included studies

A total of 22 studies, consisting of 4380 patients, were selected for this meta-analysis [Table 1]. Studies were published recently between January 24, 2020 and May 24, 2020. Individual study population size ranged between 12 and 1494 patients. Fifty-six percent of the study population were males. Median age of the patients in severe disease cohort varied from 45.2 to 67 years, whereas median age in non-severe disease cohort varied from 37 to 68.5 years. Individual symptoms studied were cough,[5-20] expectoration,[5-7,9,10,14,18,19,21] fever,[5-21] breathlessness,[5-11,13-21] hemoptysis,[5,6] sore throat,[5,7,9,10,15,16,18,21] fatigue,[5,6,9-11,13,14,16-18] myalgia,[6,7,9,10,12,16,18,19,21] headache,[5-10,12,16,18,21] nausea/vomiting,[5,9,11,12,16,18,21] diarrhea,[5,7,9,11,12,15-18,21] abdominal pain,[9,11] anorexia,[9,11] and anosmia.[16,18] The various comorbidities studied were chronic obstructive pulmonary disease (COPD)[5-7,9,11,12,16-19,21-26] diabetes[5,6,7,9,11-14,16-19,21-26] obesity,[16,18,22] hypertension,[5-7,9,11-14,16-19,21-23,25,26] cardiovascular disease (CVD), [5-7,9,11-14,16-19,21,22,24,25] cerebrovascular accidents,[5,9,11,16,18,19,21,24] chronic kidney disease (CKD),[5,9,11,12,16,18,21,24-26] chronic liver disease,[6,9,11,19,21,24] malignancy,[5,6,9,16,17,19,21,23,26] and immunocompromised state.[5,18,24] Majority of the studies (13) were from China,[5-14,22,23,26] however, three studies were from the United States,[16,18,24] two from Italy[17,21] and one each from Singapore,[15] Norway,[20] South Korea[19] and Israel.[25] Each study was retrospective observational in design. The number of clinical characteristics including comorbidities reported in each study, varied from 3 in one study[20] to 21 in another study.[5] Patients with severe disease were older compared to those with non-severe disease (59.8 years vs. 50.8 years, $P = 0.008$). According to the WHO-China joint mission,[2] severe disease was defined as tachypnea (≥30 breaths/min) or oxygen saturation ≤ 93% at rest, or ratio of arterial oxygen saturation and fraction of inspired oxygen < 300 mmHg, and critical disease was defined as respiratory failure requiring mechanical ventilation, shock, or other organ failure that requires intensive care. Severe/critical disease were considered "Severe" in most of the studies.[5,7,8,10,12,16,23] Intensive care unit (ICU)

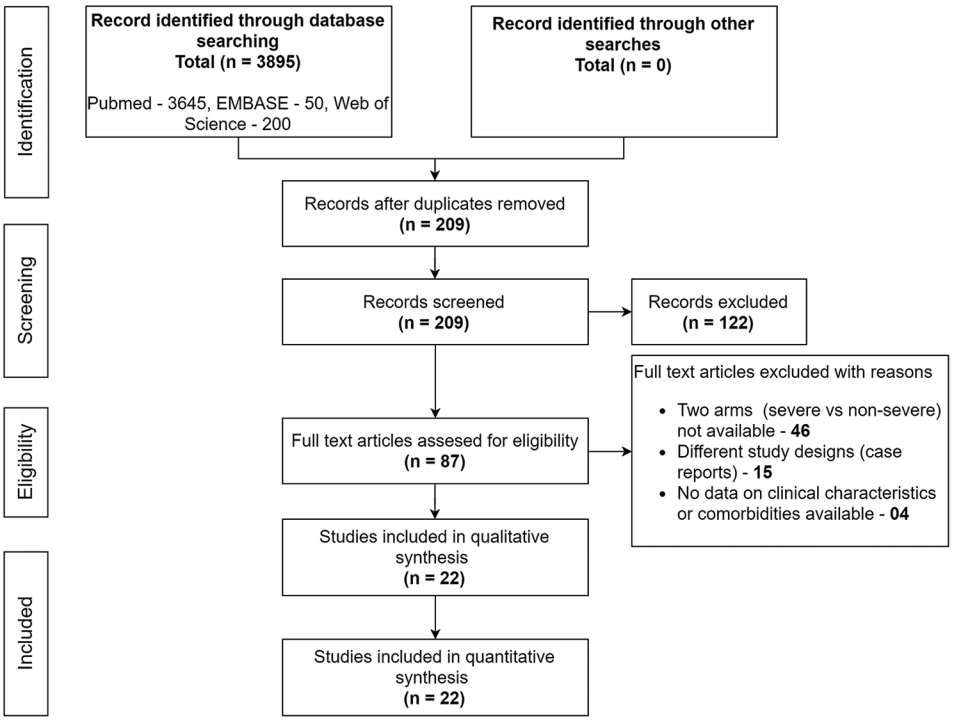

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram

admission was considered as "Severe/critical disease" in six studies.[18-21,24,25] Results of quality assessment of the included studies are summarized as AXIS scores in Table 1. Overall quality of studies was good, with thirteen out of twenty-two studies having scores above average (score ≥ 15).

Quantitative data synthesis results

ORs of severe disease were pooled for each of the individual symptoms and comorbidities. Forest plots of pOR and funnel plots for each of the clinical determinants are depicted in Supplementary Figures S1-S50. Table 2 and Figure 2 summarizes the pOR for each clinical determinant (clinical feature at admission and comorbidities). Severe disease was more common in males than females (pOR: 1.36, 95% CI: 1.08–1.70). Clinical features associated with significantly higher odds of disease severity were abdominal pain (pOR: 6.58, 95% CI: 1.56–27.67) and breathlessness (pOR: 3.94, 95% CI: 2.55–6.07). Fever (pOR: 1.48, 95% CI: 1.19–1.85) and hemoptysis (pOR: 3.35, 95% CI: 1.05–10.74) were also associated with severe disease, although their lower confidence levels were approaching near one. Patients with comorbidities were also at higher odds of presenting with severe COVID-19 disease. pOR was highest for COPD (pOR: 2.92, 95% CI: 1.70–5.02), followed by obesity (pOR: 2.84, 95% CI: 1.19–6.77), malignancy (pOR: 2.38, 95% CI: 1.25–4.52), diabetes (pOR: 2.29, 95% CI: 1.56–3.39), hypertension (pOR: 1.72, 95% CI: 1.23–2.42), CVD (pOR: 1.61, 95% CI: 1.31–1.98) and CKD (pOR: 1.46, 95% CI: 1.06–2.02). With the exception of the studies considered for breathlessness, nausea/vomiting, anorexia, and diabetes, none of the studies included in the meta-analysis for comorbidities had statistical heterogeneity ($I^2 < 50\%$). Funnel plot analyses [Supplementary Figures: S1-S50] and Egger's regression [Table 2] demonstrated the evidence of publication bias in the meta-analysis of studies focussing on fever, COPD and CVD.

Discussion

COVID-19 is a rapidly progressing pandemic affecting millions of people worldwide. With the surge of cases, it is expected to overwhelm health-care systems, thereby making it important for physicians to identify clinical characteristics that could point toward progression-to-severe illness. In our meta-analysis of 4380 patients, we found that patients presenting with complaints of breathlessness, hemoptysis and/or abdominal pain, and comorbidities had significantly higher odds of having severe disease.

Multiple studies have shown that patients with breathlessness on arrival had a higher likelihood development of acute respiratory distress syndrome and ICU requirements.[7,14,9] In studies conducted by Guan *et al*. and Huang *et al*., the incidence of hemoptysis was higher among patients with severe disease as compared to that of non-severe disease, although its proportion was lower in both the study groups.[5,6] In a study by Zhang *et al*., few COVID-19 patients presented with atypical abdominal pain and were initially admitted to the surgical ward but subsequently required ICU. These patients were presumed to infect others during their hospital stay, and the newly infected patients also had abdominal pain at presentation. Hence, some authors have suggested the gastrointestinal tract as an alternative route for viral transmission.[27] Hence, it is

Table 1: Characteristics of the included studies

Author	Publication date	Country	Sample size			Age (median, IQR)		Male (%)		Clinical characteristics included		Definition of severity	Quality of study (score out of 20)**
			Total	Severe	Nonsevere	Severe	Nonsevere	Severe	Nonsevere	Numbers	Characteristics*		
Huang C	January 24, 2020	China	41	13	28	49 (41-61)	49 (41-57.5)	85	68	13	a, b, c, d, e, g, i, n, o, p, q, t, v	Requiring ICU care	16
Wang D	February 07, 2020	China	138	36	102	66 (57-78)	51 (37-62)	61.1	52	20	a, b, c, d, f, g - t, v	Requiring ICU care	16
Liu Y	February 09, 2020	China	12	6	6	64	43.5	50	83.3	11	a, c, h, i, j, k, n, o, p, q, s	Severe and critical disease	12
Zhang J	February 18, 2020	China	140	58	82	64 (25-87)	51.5 (26-78)	56.9	46.3	16	a, c, d, g, j, k, l, m, n - t	Severe and critical disease	15
Xu Y	February 21, 2020	China	50	13	37	NA	NA	54	59.5	8	a, b, c, d, f, g, h, i	Severe and critical disease	14
Tian S	February 27, 2020	China	262	46	216	61.4 (1-94)	44.5 (1-93)	56.5	46.8	4	a, c, d, i	Severe and critical disease	16
Guan W	February 28, 2020	China	1099	173	926	52 (40-65)	45 (34-57)	57.8	58.2	21	a - s, v, w	Severe and critical disease	16
Liu W	February 28, 2020	China	78	11	67	66 (51-70)	37 (32-41)	63.6	47.8	4	n, o, p, v	Clinical deterioration to severe or critical disease or death	16
Li K	February 29, 2020	China	83	25	58	53.7 (12.3)	41.9 (10.6)	60	50	12	a, b, c, d, f, h, i, k, n, o, p, q	Severe and critical disease	16
Yudong P	March 02, 2020	China	112	16	96	57.5 (54-63)	62 (55-67.5)	56.25	45.83	7	a, c, d, g, o, p, q	Critical disease	15
Young B	March 03, 2020	Singapore	18	6	12	56 (47-73)	37 (31-56)	33	58	5	a, c, d, f, k	Requiring supplemental oxygen	12
Wu C	March 13, 2020	China	201	84	117	58.5 (50-69)	48 (40-54)	71.4	58.1	8	a, b, c, d, g, o, p, q	Acute respiratory distress syndrome	17
Gao Y	March 17, 2020	China	43	15	28	45.2 (7.68)	43 (14)	60	60.7	5	n, o, p, q, u	Not clear	14
Chow N (CDC US)	March 31, 2020	US	1494	457	1037	NA	NA	NA	NA	7	n, o, q, r, s, t, w	Requiring ICU care	15
Ihle-hansen H	April 10, 2020	Norway	42	9	33	71.8	66.8	NA	NA	3	a, c, d	Requiring ICU care	17
Colaneri M	April 23, 2020	Italy	44	17	27	NA	NA	76.5	55.6	10	a, c, d, g, k, n-q, v	Requirement for highflow oxygen	17
Hong K	April 24, 2020	South Korea	98	13	85	NA	NA	46.2	37.6	12	a-d, h, n-r, t, v	Requiring ICU care	16
Aggarwal S	April 29, 2020	US	16	8	8	67 (38-70)	68.5 (41-95)	63	88	18	a, b, d, f-k, x, n-s, u, v	Critical disease	14
Zhao X	April 29, 2020	China	91	30	61	NA	NA	46.7	57.4	6	n-q, s, v	Not clear	15
Lagi F	April 30, 2020	Italy	84	16	68	67 (58-71)	62 (50-72)	87.5	60.3	17	a-d, f, h-k, n-t, v	Requiring ICU care	18
Itelman E	May 01, 2020	Israel	162	26	136	NA	NA	80.8	51.9	5	n-q, s	Requiring ICU care	17
Ferguson J	May 14, 2020	US	72	21	51	57.6 (42.2-70.1)	61.7 (46.6-72.9)	61.9	49	19	a-d, f-k, x, n-s, u, w	Requiring ICU care	19

*Clinical characteristics: Clinical symptoms - a: Cough, b: Expectoration, c: Fever, d: Dyspnea, e: Hemoptysis, f-: Sore throat, g: Fatigue, h: Myalgia, i: Headache, j: Nausea or vomiting, k: Diarrhea, l-abdominal pain, m: Anorexia; n: Chronic obstructive pulmonary disease, o: Diabetes, p: Hypertension, q: Cardiovascular diseases, r: Cerebrovascular accidents, s: Chronic kidney disease, t: Chronic liver disease, u: Obesity, v: Malignancy, w: Immunodeficiency, x: Anosmia. ^Severe disease (any of the following conditions): I, respiratory distress, RR ≥30 breaths/min; II, oxygen saturation ≤93% at rest; III, PaO_2/FiO_2 ≤300 mmHg (1 mmHg=0.133 kPa); AND critical disease (any of the following conditions): I, respiratory failure and a requirement for mechanical ventilation; II, shock; III, concomitant failure of other organs and requirement for ICU monitoring and treatment[2], **Scores for each study in AXIS tool. RR: Respiratory rate, PaO_2/FiO_2: Partial pressure of oxygen/fraction of inspired oxygen, ICU: Intensive care unit, AXIS: Appraisal tool for Cross-Sectional Studies, IQR: Interquartile range, NA: Not available

Table 2: Summary of meta-analyses for each of the clinical symptoms and comorbidities that are associated with severe COVID-19 infection

Clinical characteristics	Odds ratio	Lower CL	Upper CL	Number of studies	Total patients included in meta-analysis	Prevalence of characteristics in severe disease (*n*/*N*)	Prevalence of characteristics in mild disease (*n*'/*N*')	I^2 (%)	Publication bias (Egger's *P* value)
Demographic characteristics									
Male gender	1.36	1.08	1.70	20	2844	-	-	13.4	0.16
Clinical characteristics									
Cough	1.24	0.98	1.56	17	2512	392/560	1242/1952	5.0	0.26
Expectoration	1.15	0.73	1.82	9	1866	132/394	454/1472	47.8	0.65
Fever	1.48	1.19	1.85	17	2512	369/560	1055/1952	0.0	0.03
Dyspnea	3.94	2.55	6.07	16	2500	251/554	339/1946	56.1	0.12
Hemoptysis	3.35	1.05	10.74	2	1140	5/186	7/954	0.0	NA
Sore throat	1.39	0.77	2.49	8	1560	47/298	168/1262	29.6	0.79
Fatigue	1.22	0.83	1.81	10	1913	196/439	607/1474	41.6	0.23
Myalgia	1.25	0.87	1.79	9	1652	73/311	249/1341	8.0	0.34
Headache	1.15	0.80	1.64	9	1857	44/357	174/1500	0.0	0.89
Nausea/vomiting	0.68	0.30	1.51	7	1561	29/318	104/1243	55.6	0.31
Diarrhea	1.43	0.93	2.21	10	1706	36/366	88/1340	0.0	0.74
Abdominal pain	6.58	1.56	27.67	2	278	9/94	2/184	0.0	NA
Anorexia	2.54	0.74	8.70	2	278	32/94	40/184	72.3	NA
Anosmia	0.61	0.11	3.48	2	88	2/29	5/59	0.0	NA
Comorbid illness									
Chronic obstructive pulmonary disease	2.92	1.70	5.02	16	3695	124/925	177/2770	23.3	<0.01
Diabetes	2.29	1.56	3.39	18	4008	258/1025	413/2983	50.5	0.08
Obesity	2.84	1.19	6.77	3	131	18/44	18/87	0.0	0.43
Hypertension	1.72	1.23	2.42	17	2514	182/568	412/1946	41.6	0.41
Cardiovascular disease	1.61	1.31	1.98	16	3839	199/984	372/2855	0.0	0.01
Cerebrovascular accidents	1.68	0.73	3.84	8	3141	21/782	44/2359	32.1	0.45
Chronic kidney disease	1.46	1.06	2.02	10	3308	70/831	112/2477	0.0	0.16
Chronic liver disease	1.55	0.75	3.18	6	1995	12/593	20/1402	0.0	0.90
Malignancy	2.38	1.25	4.52	9	1689	19/317	29/1372	0.0	0.81
Immunocompromised state	1.46	0.98	2.17	3	2665	42/651	70/2014	0.0	0.33

CL: Confidence limits, *n*: Number of patients with the clinical determinant among patients with severe disease, *N*: Total number of patients with severe disease, *n*': Number of patients with the clinical determinant among patients with mild disease, *N*': Total number of patients with severe disease, I^2: Heterogeneity statistics, Egger's $P<0.05$: Publication bias present

necessary to not miss abdominal pain as a rare but important predictor of severe disease. Therefore, any patient presenting with SARI with suspicion of COVID-19 and complaints of breathlessness, hemoptysis and/or abdominal pain should be admitted and evaluated further before deciding further course of treatment. These symptoms, along with fever and cough, might act as warning signs of severe disease.

In most of the included studies, the patients in the severe group had a higher median age when compared to the non-severe group, which was consistent with previous reports.[14,23] Our meta-analysis showed that patients with COPD had the highest risk of the development of severe disease, followed by obesity, malignancy, diabetes, hypertension, CVD, and CKD. A previous meta-analysis of eight studies had shown CVD, respiratory illness, and hypertension as significant predictors of severe disease.[28] The study differs in terms of the inclusion of a greater number of studies and comorbidities. A weaker immune system might explain the higher likelihood of the development of severe disease among older patients with comorbidities.

There are certain limitations of this meta-analysis. The studies included are retrospective in nature with considerable heterogeneity. Further, 13 out of 22 of the studies are from a single country. The criteria of severe disease were also not similar across all the included studies, thereby limiting the strength of our observations. We have also not included the studies exclusively reporting predictors of mortality in COVID-19 patients. Finally, it is possible that newer studies might have been published between the completion of this literature review and its publication.

Conclusion

Our analysis describes the presence of a significant association of the severe disease with the male gender and specific presenting symptoms such as breathlessness, abdominal pain, hemoptysis, fever, and cough. The presence of comorbidities, namely, COPD, CKD, diabetes, CVD and hypertension

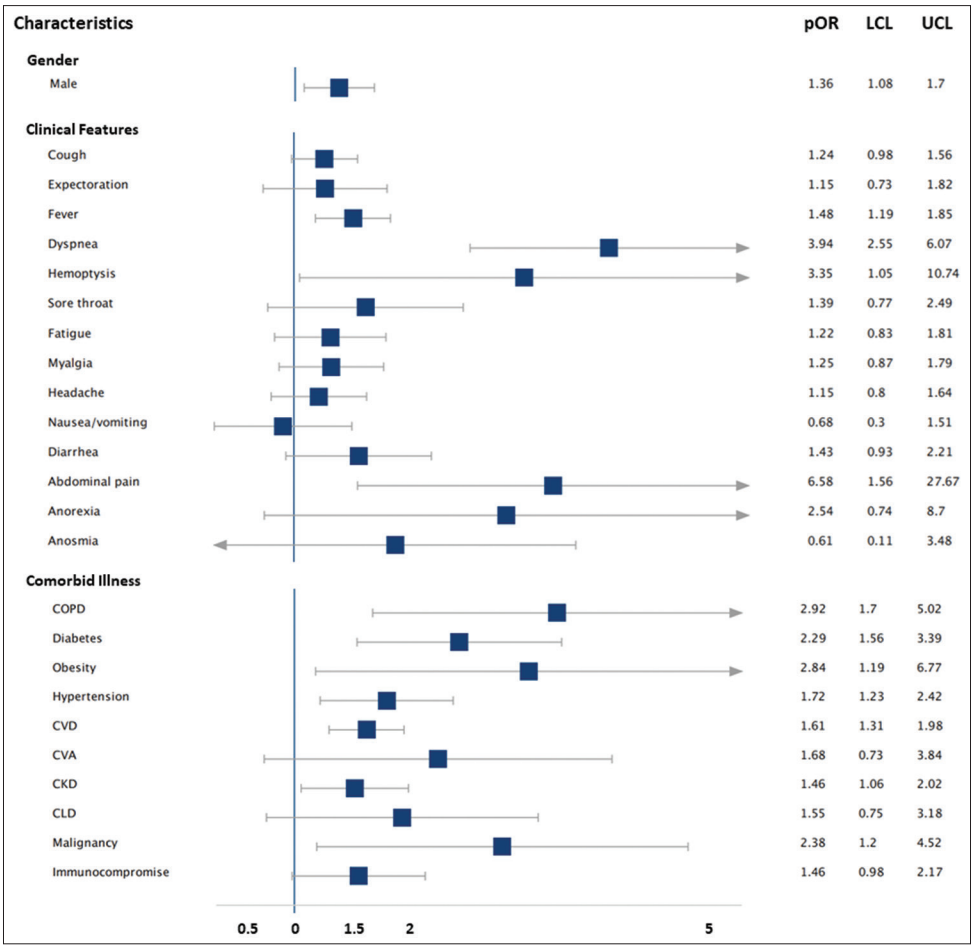

Figure 2: Summary of pooled odds ratio for each of the presenting clinical features and comorbidities. OR – pooled odds ratio, LCL – lower confidence limit of OR, UCL – upper confidence limit of OR, COPD – chronic obstructive pulmonary disease, CVD – cardiovascular diseases, CVA – cerebrovascular accidents, CLD – chronic liver disease, CKD – chronic kidney disease

were also significant risk factors for severe disease, which is in line with previous studies. Knowledge of these clinical determinants will assist the clinicians in the risk-stratification of the patients for better triage and clinical management.

What is already known on the subject

- Patients with COVID-19 presents with a wide spectrum of clinical manifestations, i.e., asymptomatic, mild upper respiratory tract symptoms, severe disease, and critical disease
- It is difficult to predict the disease progression early in the course of illness
- Multiple laboratory parameters, comorbid illness, and advanced age have been shown to predict the disease prognosis.

Study's main messages

- This updated meta-analysis consisted of 22 studies comprising 4380 patients
- Severe disease was more common in males than females
- Clinical features that were associated with significantly higher odds of severe disease were abdominal pain, breathlessness, and hemoptysis
- pOR was highest for chronic obstructive pulmonary disease, followed by obesity, malignancy, diabetes, hypertension, CVD , and CKD, for predicting severe COVID-19
- Knowledge of these clinical determinants will help the clinician to triage and manage the patients carefully, and appropriately allocate the resources in this resource-constraining pandemic.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Novel Coronavirus (2019-nCoV) Situation Reports 61; 21March, 2020. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. [Last accessed on 2020 Mar 21].
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020; 323 (13):

1239-42. https://jamanetwork.com/journals/jama/fullarticle/2762130. [Last accessed on 2020 Mar 28].
3. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, *et al*. Clinical characteristics of coronavirus disease 2019 in China. New England J Med 2020; 382 (18):1708-20. Available from: http://www.nejm.org/doi/10.1056/NEJMoa2002032. [Last accessed on 2020 Mar 24].
4. Downes MJ, Brennan ML, Williams HC, Dean RS. Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS). BMJ Open 2016;6:e011458.
5. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, *et al*. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20.
6. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
7. Li K, Wu J, Wu F, Guo D, Chen L, Fang Z, *et al*. The clinical and chest CT features associated with severe and critical COVID-19 pneumonia. Investig Radiol 2020;55:327-331.
8. Tian S, Hu N, Lou J, Chen K, Kang X, Xiang Z, *et al*. Characteristics of COVID-19 infection in Beijing. J Infect 2020;80:401-6.
9. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, *et al*. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 323 (11):1061-9.
10. Xu YH, Dong JH, An WM, Lv XY, Yin XP, Zhang JZ, *et al*. Clinical and computed tomographic imaging features of novel coronavirus pneumonia caused by SARS-CoV-2. J Infect 2020;80:394-400.
11. Zhang J, Dong X, Cao Y, Yuan Y, Yang Y, Yan Y, *et al*. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020;75:1730-41
12. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, *et al*. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci 2020;63:364-74.
13. Peng YD, Meng K, Guan HQ, Leng L, Zhu RR, Wang BY, *et al*. Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV. Zhonghua Xin Xue Guan Bing Za Zhi 2020;48:450-5.
14. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, *et al*. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020;180 (7), 934.
15. Young BE, Ong SW, Kalimuddin S, Low JG, Tan SY, Loh J, *et al*. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA 2020;323:1488.
16. Aggarwal S, Garcia-Telles N, Aggarwal G, Lavie C, Lippi G, Henry BM. Clinical features, laboratory characteristics, and outcomes of patients hospitalized with coronavirus disease 2019 (COVID-19): Early report from the United States. Diagnosis (Berl) 2020;7:91-6.
17. Colaneri M, Sacchi P, Zuccaro V, Biscarini S, Sachs M, Roda S, *et al*. Clinical characteristics of coronavirus disease (COVID-19) early findings from a teaching hospital in Pavia, North Italy, 21 to 28 February 2020. Euro Surveill 2020;25: 25 (16):2000460
18. Ferguson J, Rosser JI, Quintero O, Scott J, Subramanian A, Gumma M, *et al*. Characteristics and outcomes of coronavirus disease patients under nmonsurge conditions, Northern California, USA, March-April 2020. Emerg Infect Dis 2020;26:1679-85.
19. Hong KS, Lee KH, Chung JH, Shin KC, Choi EY, Jin HJ, *et al*. Clinical features and outcomes of 98 patients hospitalized with SARS-CoV-2 infection in Daegu, South Korea: A brief descriptive study. Yonsei Med J 2020;61:431-7.
20. Ihle-Hansen H, Berge T, Tveita A, Rønning EJ, Ernø PE, Andersen EL, *et al*. COVID-19: Symptoms, course of illness and use of clinical scoring systems for the first 42 patients admitted to a Norwegian local hospital. Tidsskrift Den Norske Legeforening 2020 [Ahead of print], doi-10.4045/tidsskr. 20.0301
21. Lagi F, Piccica M, Graziani L, Vellere I, Botta A, Tilli M, *et al*. Early experience of an infectious and tropical diseases unit during the coronavirus disease (COVID-19) pandemic, Florence, Italy, February to March 2020. Euro Surveill 2020;25: 25 (17):2000556.
22. Gao Y, Li T, Han M, Li X, Wu D, Xu Y, *et al*. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virol 2020;92:791-96
23. Liu W, Tao ZW, Lei W, Ming-Li Y, Kui L, Ling Z, *et al*. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J 2020;133:1032-38
24. Chow N, Fleming-Dutra K, Gierke R, Hall A, Hughes M, Pilishvili T, *et al*. Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019 United States, February 12–March 28, 2020. MMWR Morb Mortal Wkly Rep 2020;69:382-6.
25. Itelman E, Wasserstrum Y, Segev A, Avaky C, Negru L, Cohen D, Turpashvili N, Anani S, Zilber E, Lasman N, Athamna A. Clinical characterization of 162 COVID-19 patients in Israel: preliminary report from a large tertiary center. The Israel Medical Association journal: IMAJ. 2020 May 1;22 (5).
2 6. Zhao XY, Xu XX, Yin HS, Hu QM, Xiong T, Tang YY, *et al*. Clinical characteristics of patients with 2019 coronavirus disease in a non-Wuhan area of Hubei Province, China: A retrospective study. BMC Infect Dis 2020;20:1-8
27. Zhang H, Kang Z, Gong H, Xu D, Wang J, Li Z, *et al*. The digestive system is a potential route of 2019-nCov infection: A bioinformatics analysis based on single-cell transcriptomes. bioRxiv Cold Spring Harbor Lab. 2020.01.30.927806; doi: https://doi.org/10.1101/2020.01.30.927806
28. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, *et al*. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: A systematic review and meta-analysis. Int J Infect Dis 2020;94:91-95

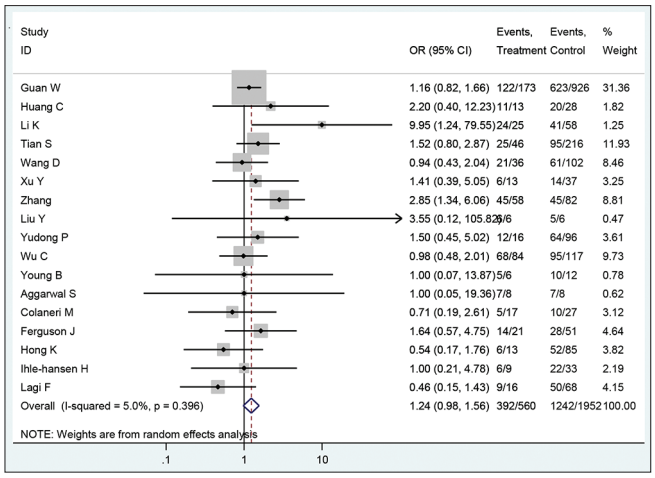

Figure S1: Forest plot of odds ratio for cough as a predictor of disease severity

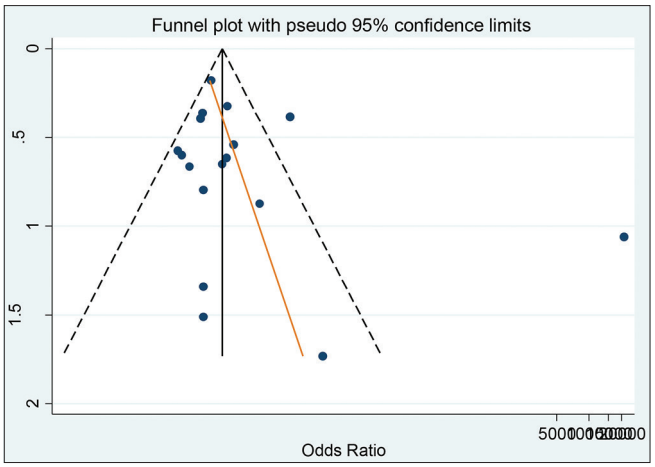

Figure S2: Funnel plot of odds ratio for cough as a predictor of disease severity

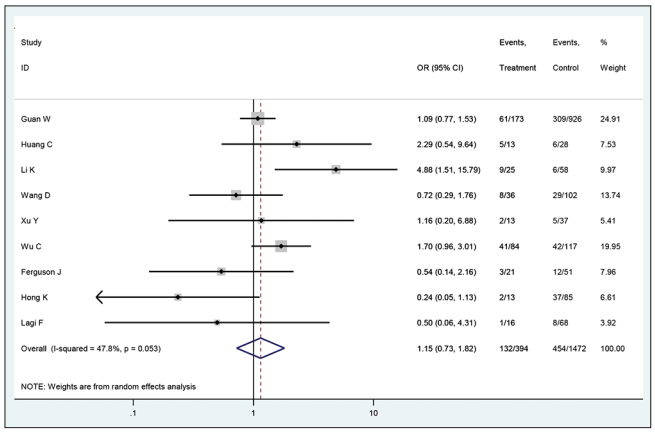

Figure S3: Forest plot of odds ratio for expectoration as a predictor of disease severity

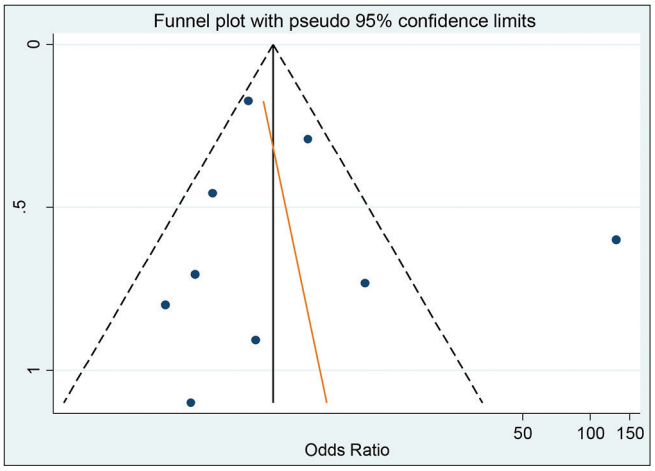

Figure S4: Funnel plot of odds ratio for expectoration as a predictor of disease severity

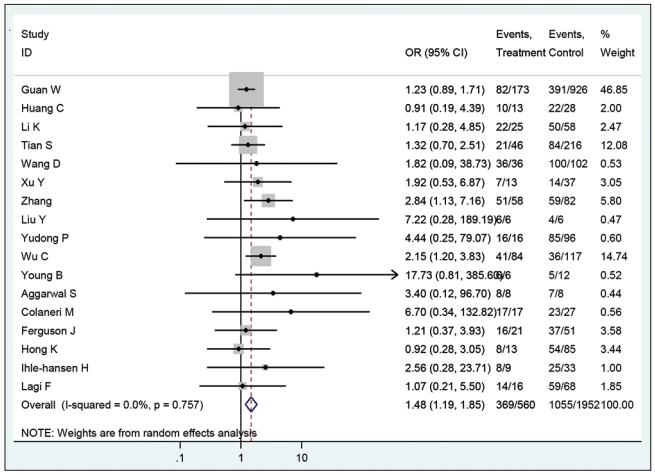

Figure S5: Forest plot of odds ratio for fever as a predictor of disease severity

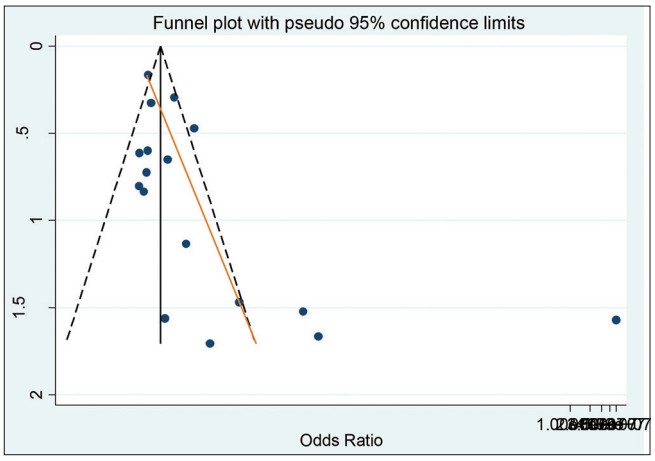

Figure S6: Funnel plot of odds ratio for fever as a predictor of disease severity

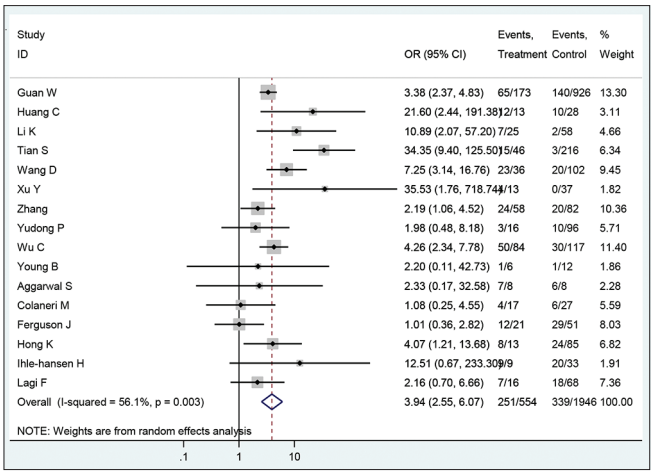

Figure S7: Forest plot of odds ratio for dyspnea as a predictor of disease severity

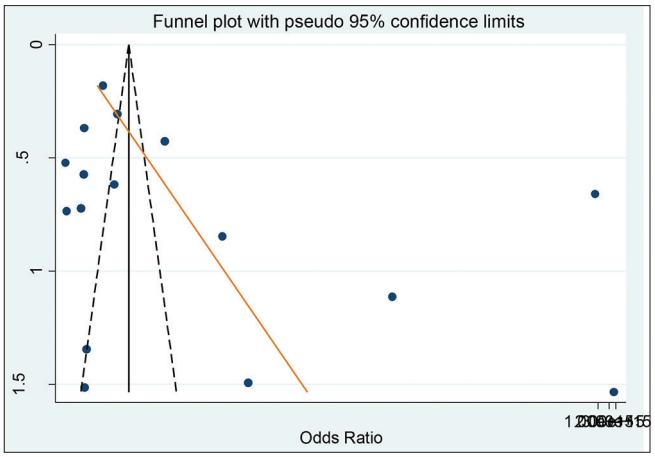

Figure S8: Funnel plot of odds ratio for dyspnea as a predictor of disease severity

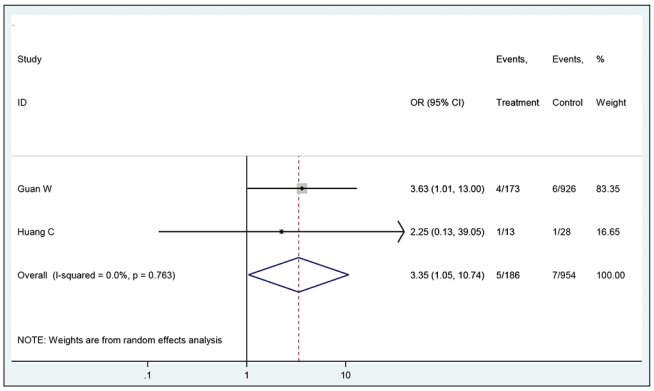

Figure S9: Forest plot of odds ratio for hemoptysis as a predictor of disease severity

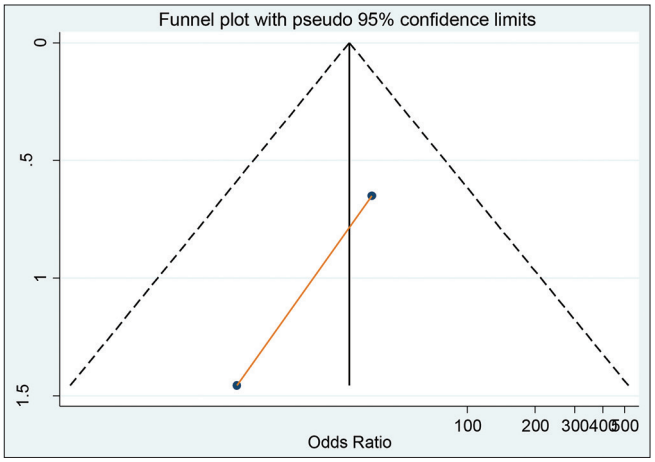

Figure S10: Funnel plot of odds ratio for hemoptysis as a predictor of disease severity

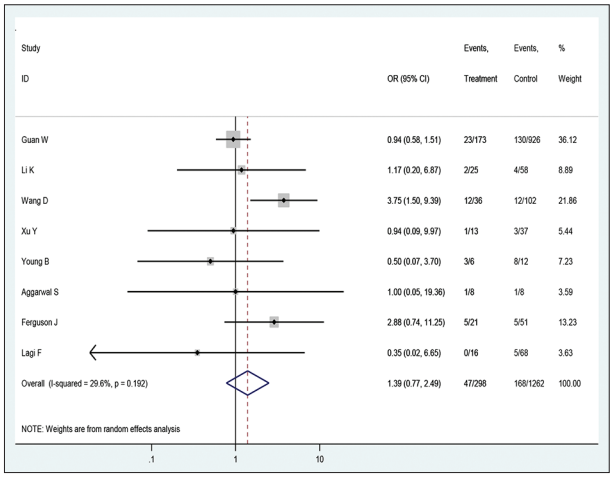

Figure S11: Forest plot of odds ratio for sore throat as a predictor of disease severity

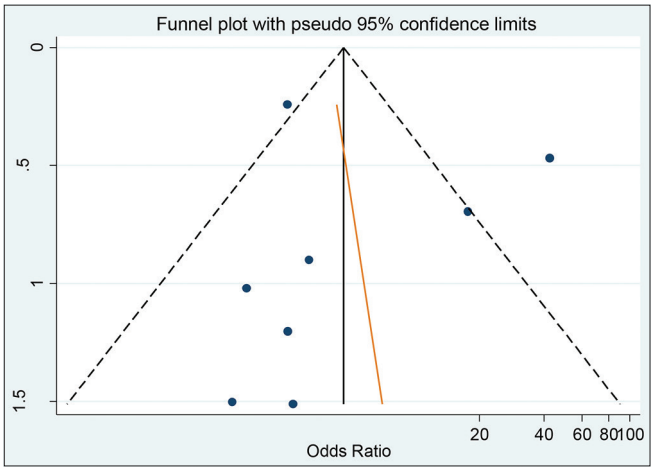

Figure S12: Funnel plot of odds ratio for sore throat as a predictor of disease severity

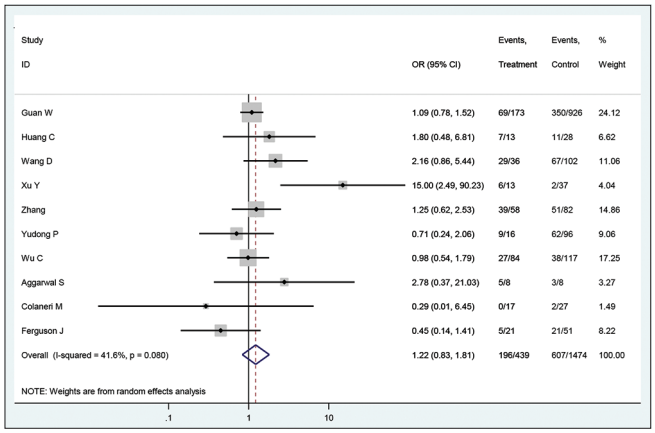

Figure S13: Forest plot of odds ratio for fatigue as a predictor of disease severity

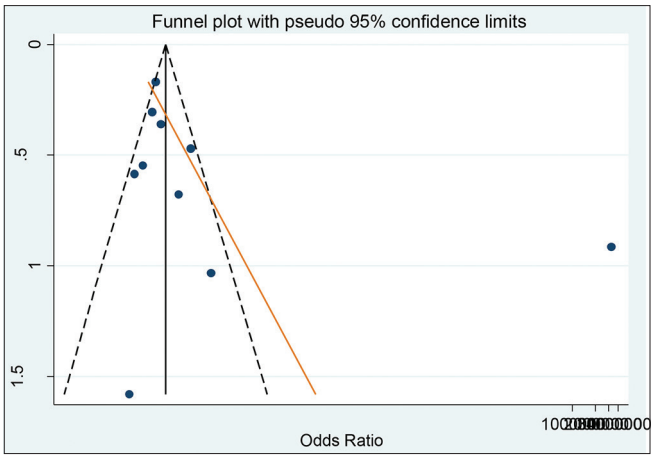

Figure S14: Funnel plot of odds ratio for fatigue as a predictor of disease severity

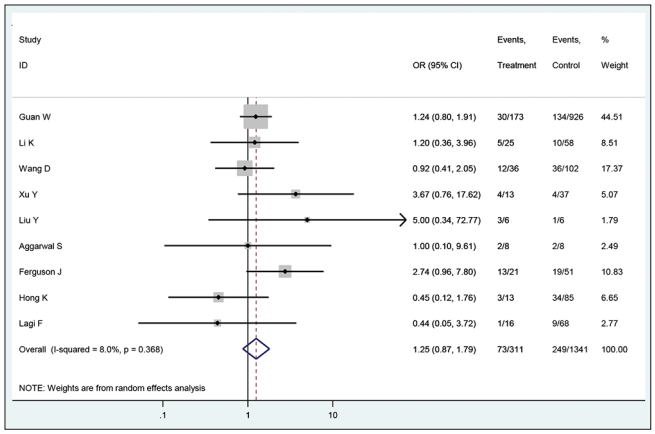

Figure S15: Forest plot of odds ratio for myalgia as a predictor of disease severity

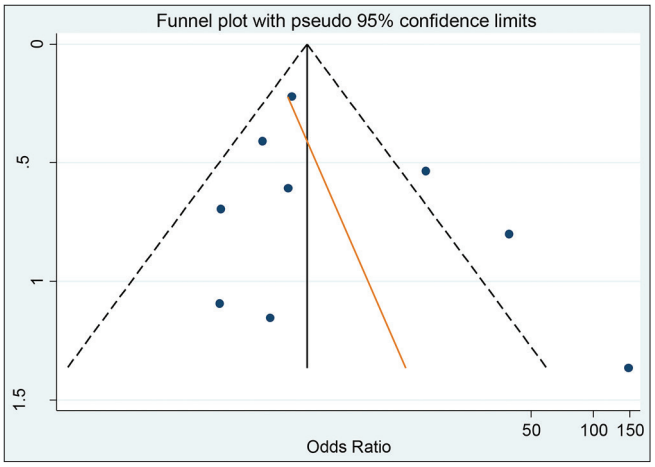

Figure S16: Funnel plot of odds ratio for myalgia as a predictor of disease severity

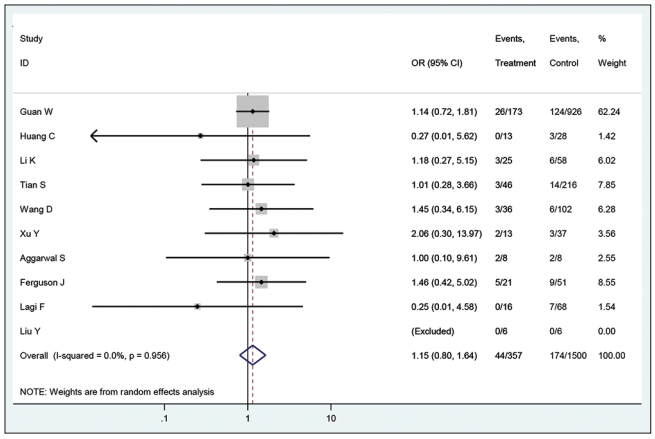

Figure S17: Forest plot of odds ratio for headache as a predictor of disease severity

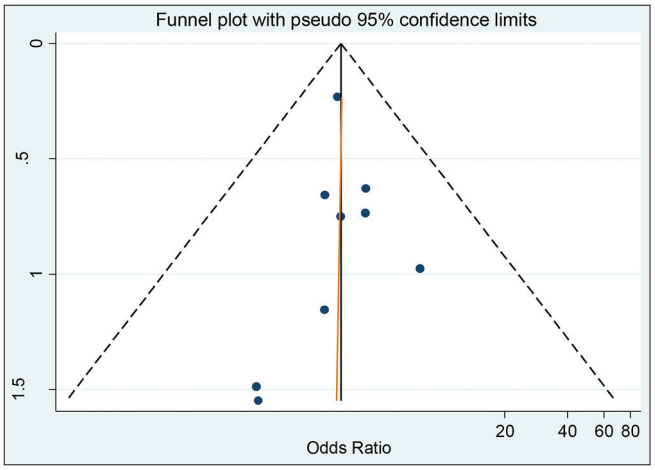

Figure S18: Funnel plot of odds ratio for headache as a predictor of disease severity

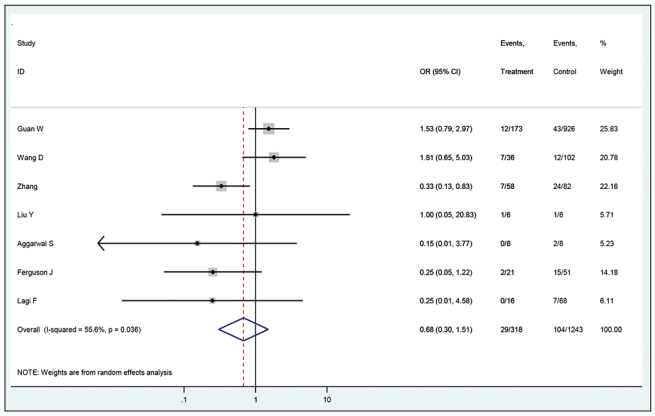

Figure S19: Forest plot of odds ratio for nausea / vomiting as a predictor of disease severity

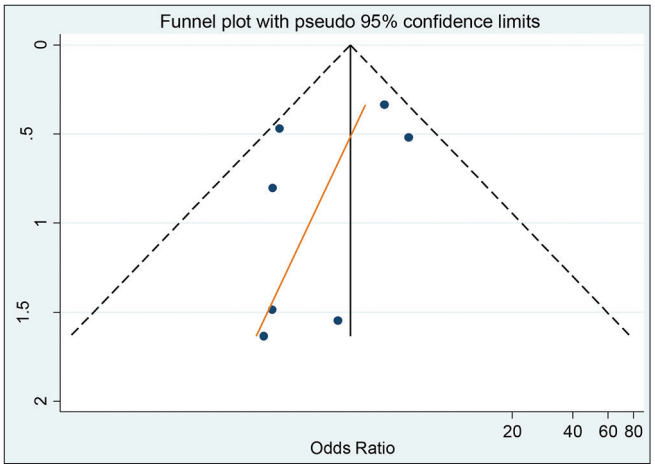

Figure S20: Funnel plot of odds ratio for nausea / vomiting as a predictor of disease severity

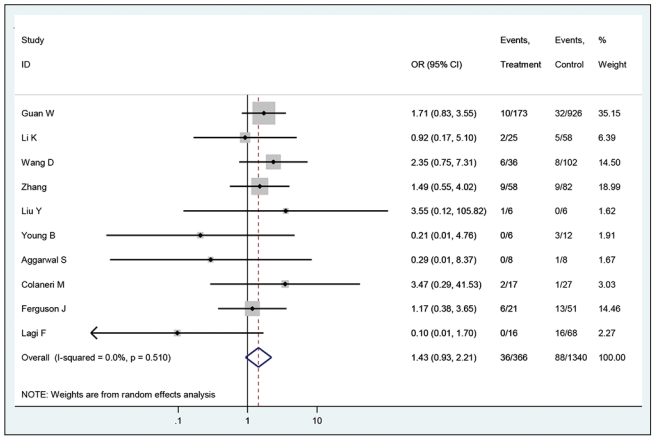

Figure S21: Forest plot of odds ratio for diarrhea as a predictor of disease severity

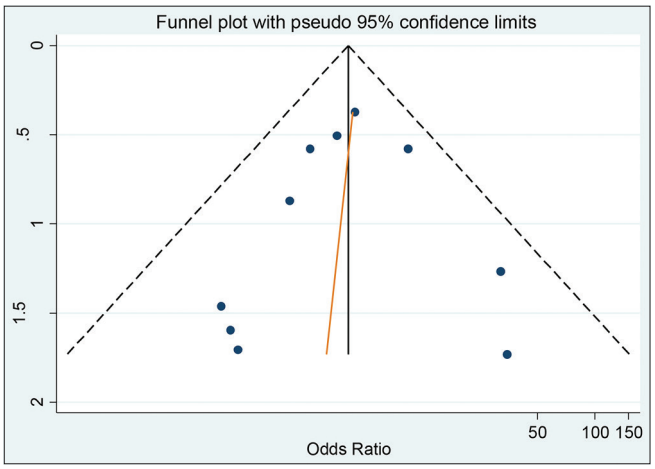

Figure S22: Funnel plot of odds ratio for diarrhea as a predictor of disease severity

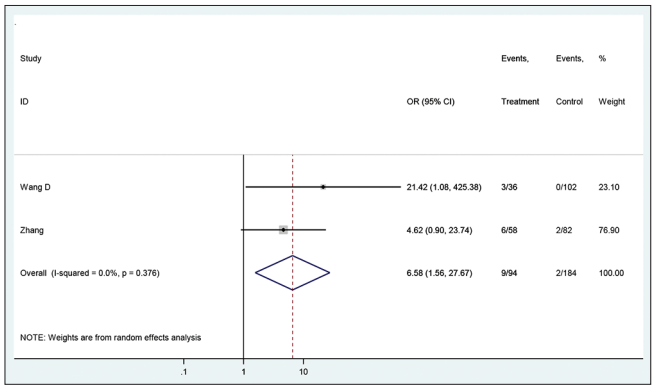

Figure S23: Forest plot of odds ratio for abdominal pain as a predictor of disease severity

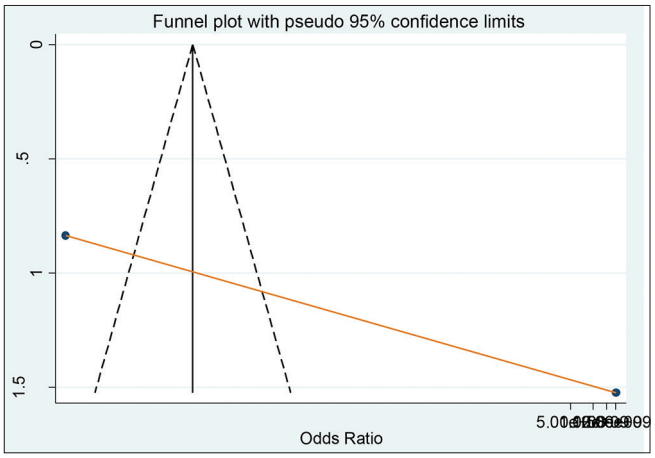

Figure S24: Funnel plot of odds ratio for abdominal pain as a predictor of disease severity

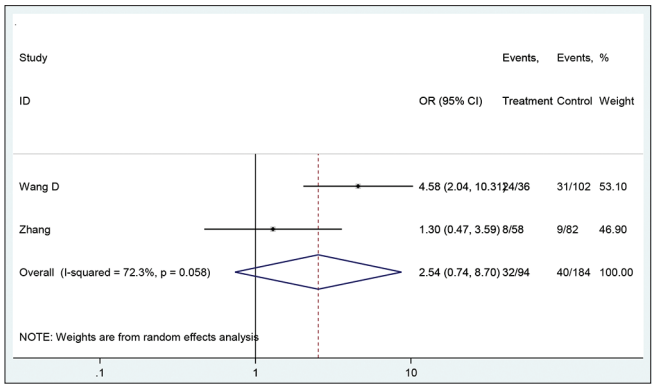

Figure S25: Forest plot of odds ratio for anorexia as a predictor of disease severity

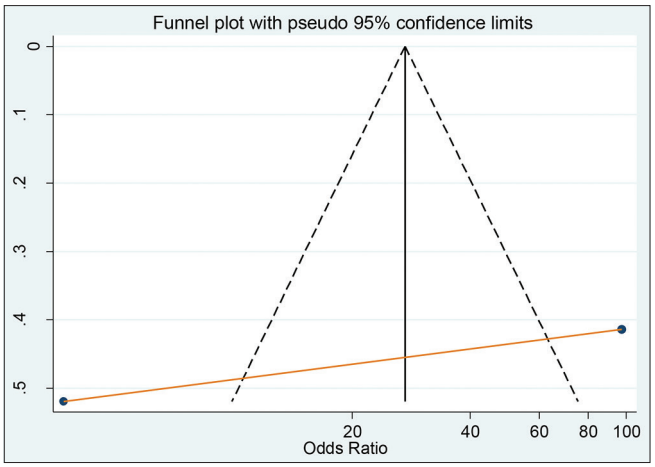

Figure S26: Funnel plot of odds ratio for anorexia as a predictor of disease severity

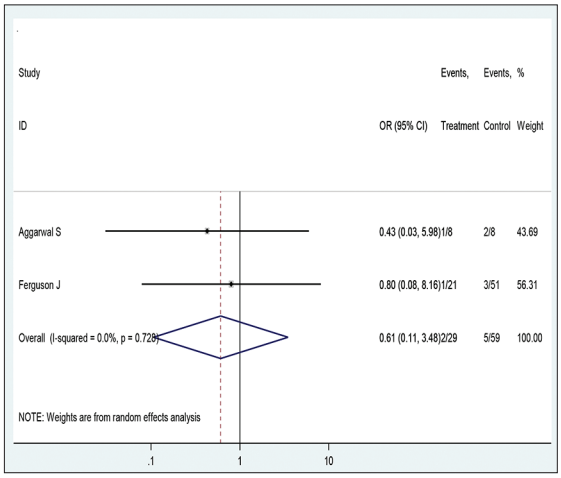

Figure S27: Forest plot of odds ratio for anosmia as a predictor of disease severity

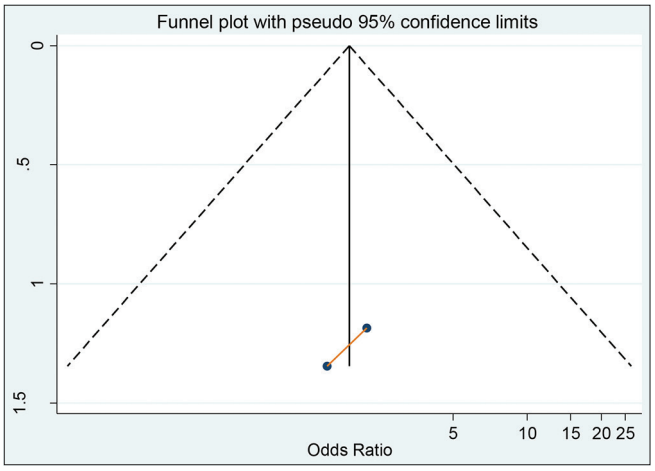

Figure S28: Funnel plot of odds ratio for anorexia as a predictor of disease severity

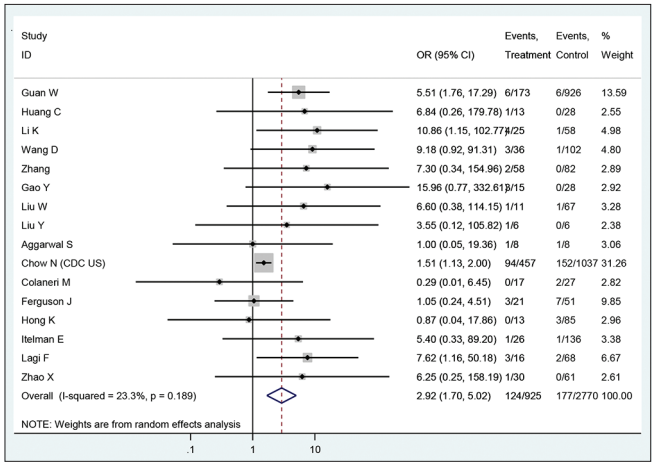

Figure S29: Forest plot of odds ratio for COPD as a predictor of disease severity

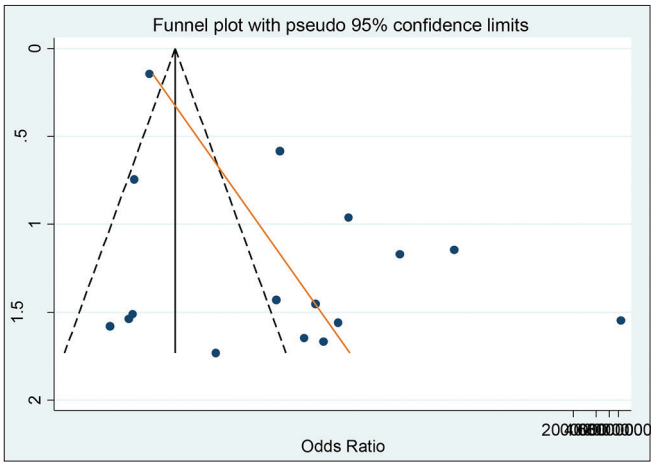

Figure S30: Funnel plot of odds ratio for COPD as a predictor of disease severity

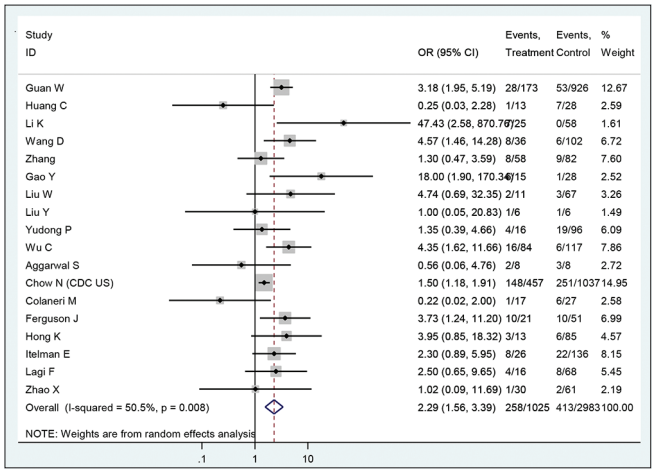

Figure S31: Forest plot of odds ratio for diabetes as a predictor of disease severity

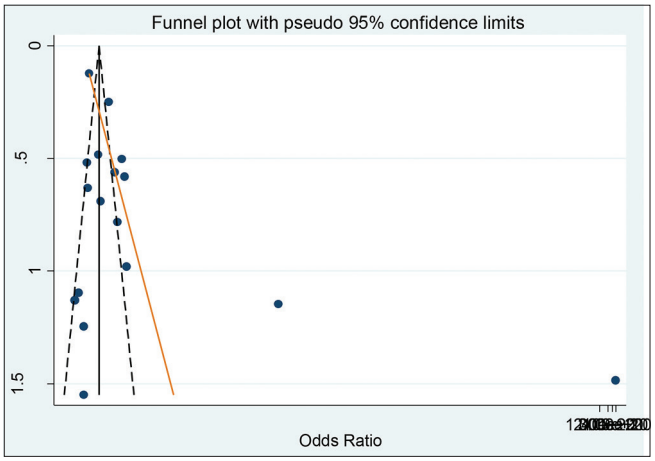

Figure S32: Funnel plot of odds ratio for diabetes as a predictor of disease severity

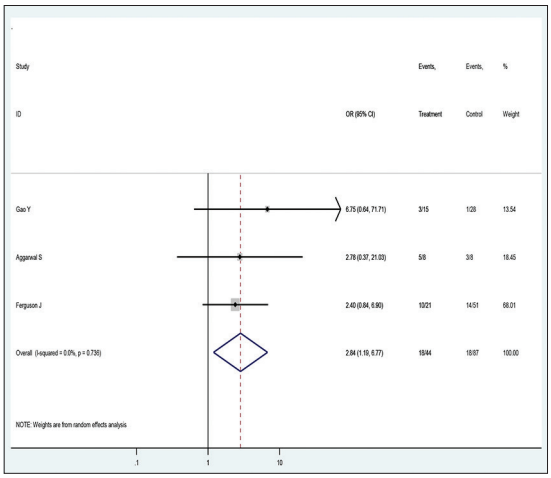

Figure S33: Forest plot of odds ratio for obesity as a predictor of disease severity

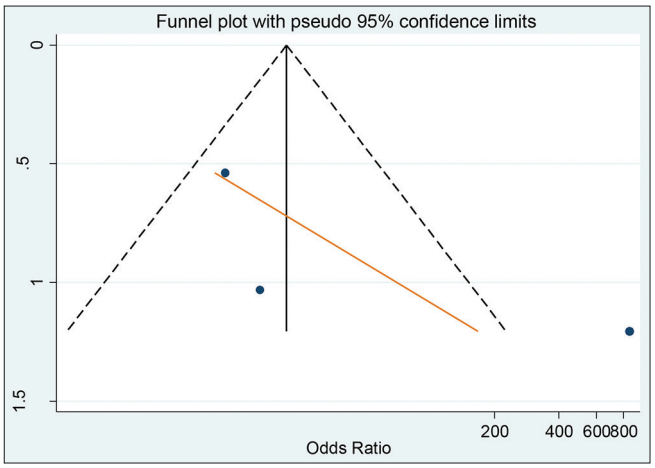

Figure S34: Funnel plot of odds ratio for obesity as a predictor of disease severity

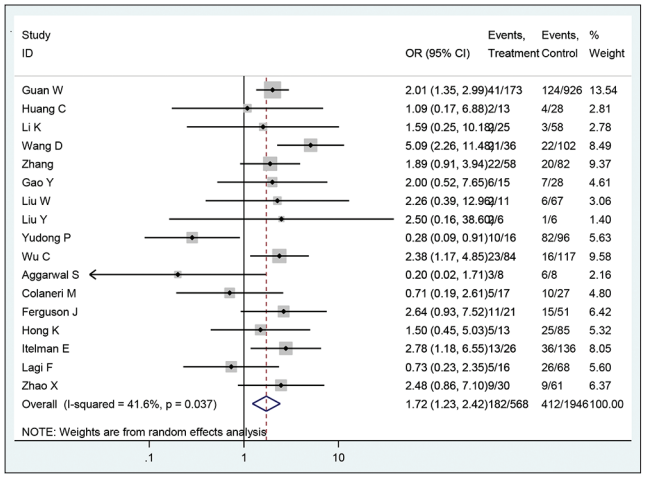

Figure S35: Forest plot of odds ratio for hypertension as a predictor of disease severity

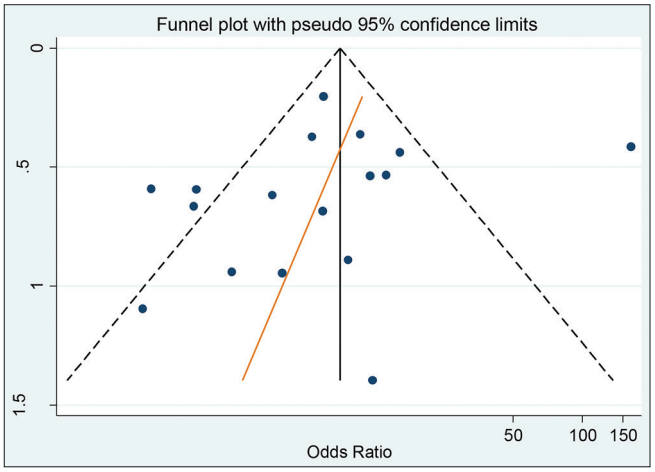

Figure S36: Funnel plot of odds ratio for hypertension as a predictor of disease severity

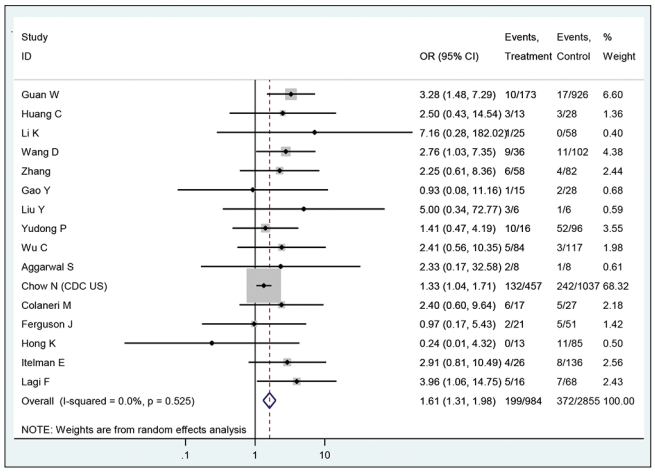

Figure S37: Forest plot of odds ratio for cardiovascular diseases as a predictor of disease severity

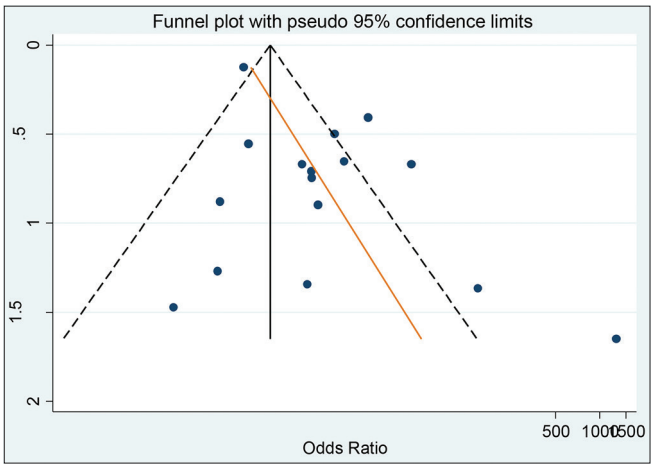

Figure S38: Funnel plot of odds ratio for cardiovascular diseases as a predictor of disease severity

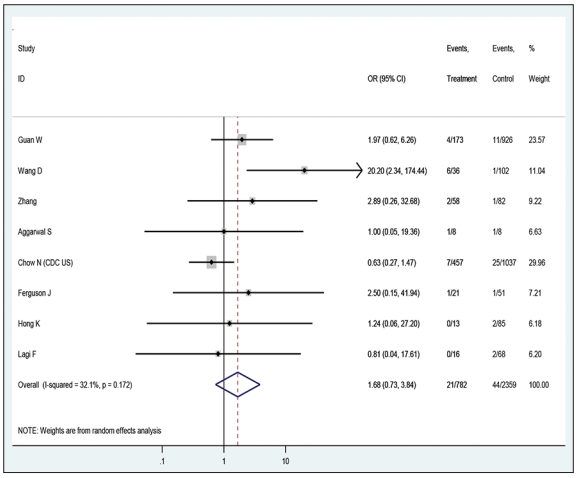

Figure S39: Forest plot of odds ratio for cerebrovascular accidents as a predictor of disease severity

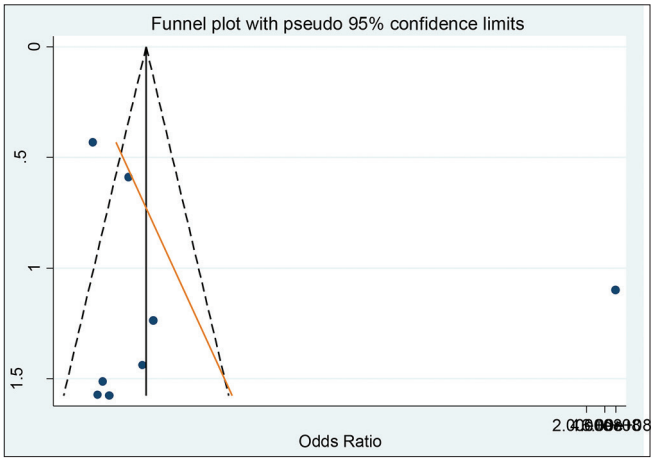

Figure S40: Funnel plot of odds ratio for cerebrovascular accidents as a predictor of disease severity

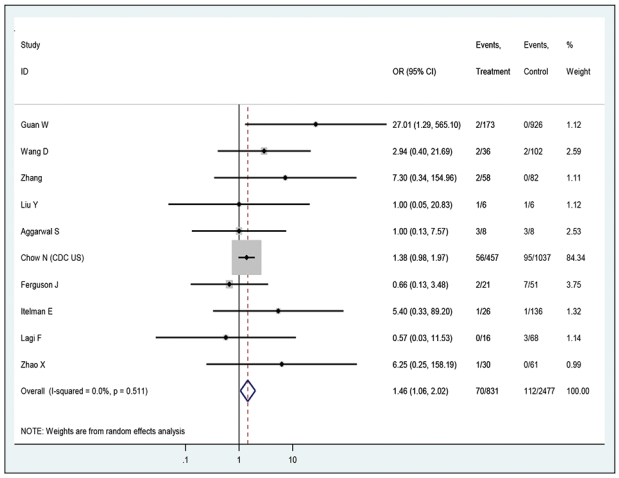

Figure S41: Forest plot of odds ratio for CKD as a predictor of disease severity

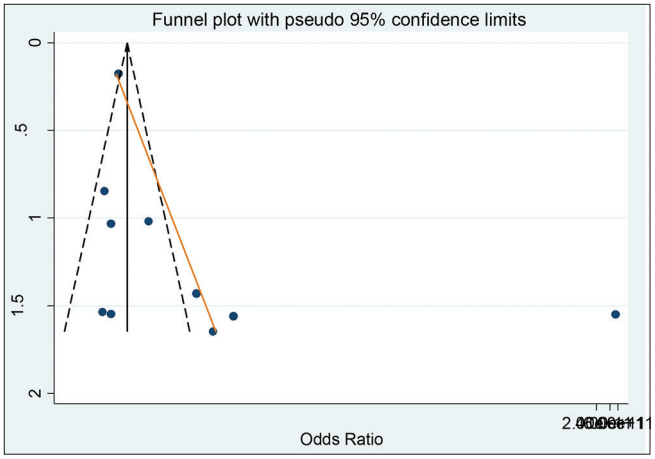

Figure S42: Funnel plot of odds ratio for CKD as a predictor of disease severity

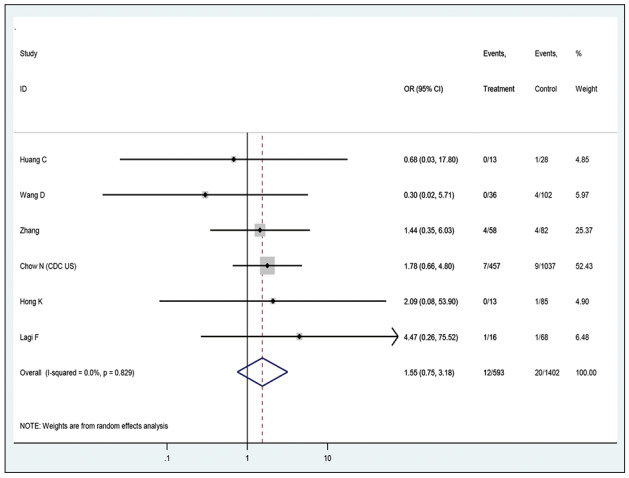

Figure S43: Forest plot of odds ratio for chronic liver disease as a predictor of disease severity

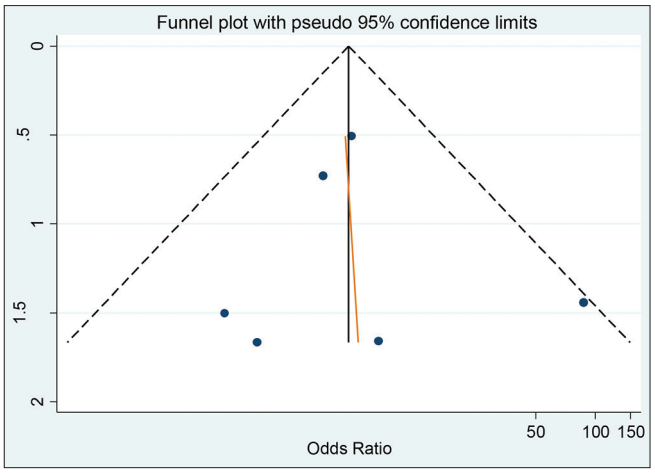

Figure S44: Funnel plot of odds ratio for chronic liver disease as a predictor of disease severity

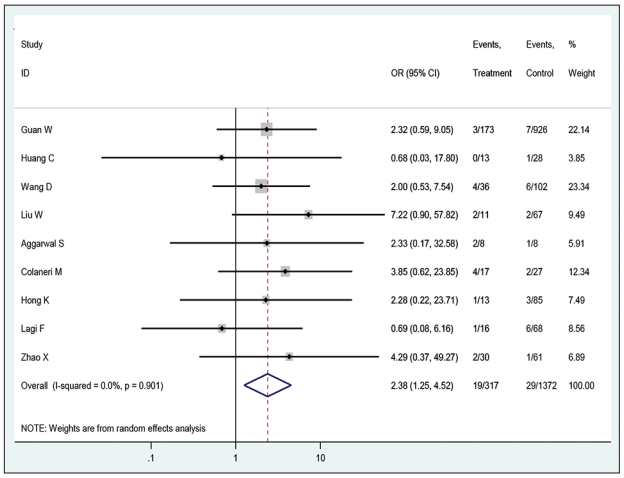

Figure S45: Forest plot of odds ratio for malignancy as a predictor of disease severity

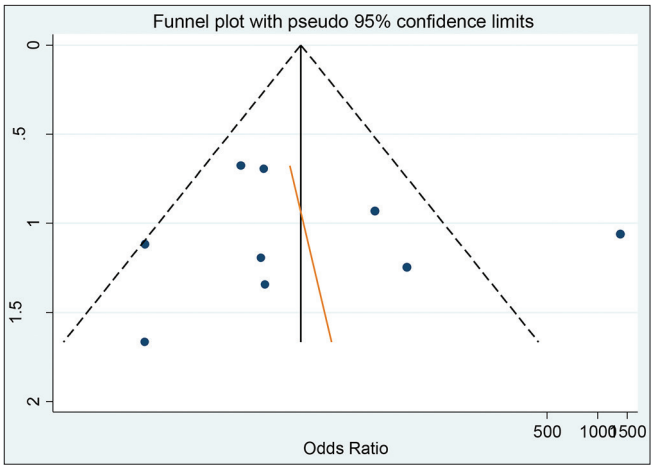

Figure S46: Funnel plot of odds ratio for chronic liver disease as a predictor of disease severity

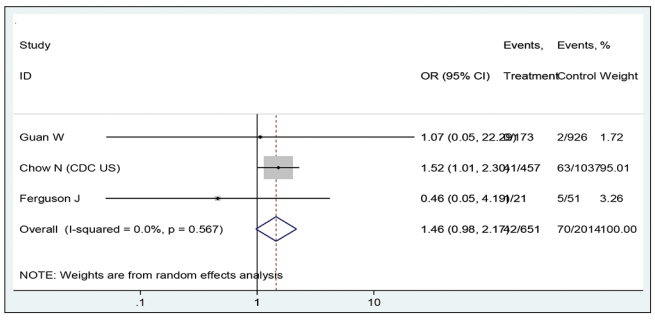

Figure S47: Forest plot of odds ratio for immunocompromised state as a predictor of disease severity

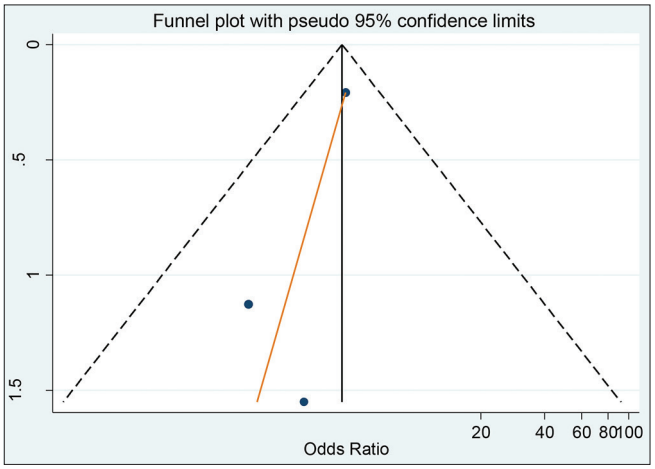

Figure S48: Funnel plot of odds ratio for immunocompromised state as a predictor of disease severity

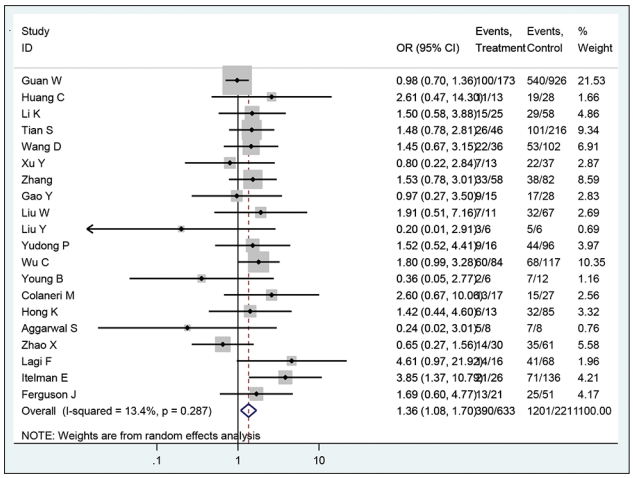

Figure S49: Forest plot of odds ratio of gender for disease severity

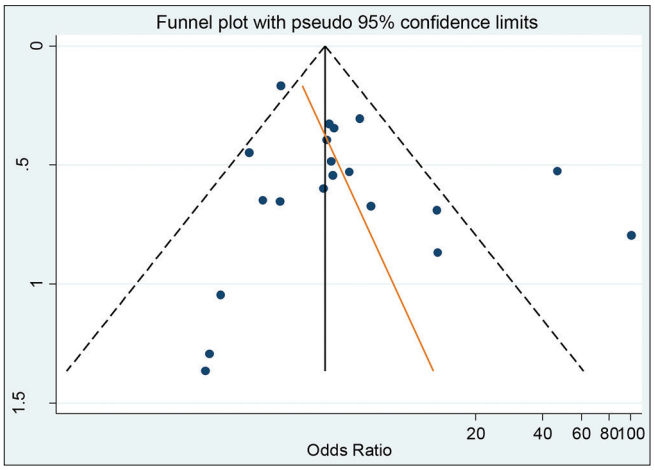

Figure S50: Funnel plot of odds ratio of gender for disease severity