Comparison of clinical characteristics and risk factors in hospitalized patients with SARS-CoV-2, MERS-CoV, and SARS-CoV infection

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Research

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Abstract

Herein, we compared the risk factors, clinical presentation of patients hospitalized with SARS-CoV-2, SARS-CoV, or MERS-CoV infection. The proportion of male patients with COVID-19 was higher than who with SARS but lower than who with MERS ($p<0.001$). More patients with COVID-19 had coexisting chronic medical conditions than those with SARS ($p<0.001$) but fewer than those with MERS ($p<0.001$), and the prevalence of hypertension (17%) and smoking history (14%) was higher than in patients with SARS ($p<0.001$). Furthermore,the symptom of fever (53%), hemoptysis (1%), diarrhea (4%) and vomiting (3%) of COVID-19 were significantly lower than that in patients with SARS or MERS. The level of ALT and AST in COVID-19 was significantly lower ($p<0.001$), however, thrombocytopenia, high LDH were common. Summary, male, smoking history and hypertension were the most common risk factors for hospitalization with COVID-19; and the clinical feature was less severe in COVID-19.

Background

Coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a newly recognized illness that first appeared in Wuhan (Hubei Province), China and has since spread rapidly to other provinces in China and around the world [1–3]. Coronaviruses (CoVs) are enveloped RNA viruses that are widely distributed in humans, other mammals, and birds and that cause respiratory, intestinal, liver, and neurological diseases [2, 4]. There are seven CoV types known to be associated with human disease; four of these strains, including 229E, OC43, NL63 and HKU1, usually cause the common cold [5]. However, the other three types of CoV, severe acute respiratory syndrome-associated coronavirus (SARS-CoV) [6], Middle East respiratory syndrome-associated coronavirus (MERS-CoV) [7], and SARS-CoV-2 are highly pathogenic, leading to severe pneumonia and even death. World Health Organization (WHO) statistics at the time containment of the outbreak of SARS-CoV was announced on July 5, 2003 indicated that a total 8096 cases of SARS and 774 deaths were reported across 29 countries, with an overall case-fatality rate (CFR) of 9.6%. MERS-CoV infection has not yet been contained and is thus far responsible for 2494 confirmed cases and 858 deaths across 27 countries, with a CFR of 34.4% [8]. As of March 13, 2020, the WHO announced that SARS-CoV-2 infection had affected a cumulative number of 132,758 people worldwide and led to 2009 deaths [9]; the CFR was estimated to be about 3.7%. Although the estimated CFR for COVID-19 is not much higher than those of SARS and MERS, COVID-19 has led to more total deaths owing to a larger number of cases. Thus, infection with these CoVs merits urgent attention.

Similarities and differences have been reported among SARS-CoV-2, SARS-CoV, and MERS-CoV. First, viral gene sequencing of SARS-CoV-2 affecting the first patients has shown a 79.5% similarity with SARS [10]; in addition, as with SARS-CoV, bats and minks are potential hosts of SARS-CoV-2 [11]. Second, the estimated mean value of the basic regeneration index (R0) of SARS-CoV-2 is 3.28, which is much higher than those of SARS-CoV and MERS-CoV; thus, the transmissibility of SARS-CoV-2 appears to be much higher, thereby leading to a larger number of cases [12]. Furthermore, the incubation period of SARS is 4.5 (2–12) days and that of MERS is 4 (2–14) days; the estimated incubation period of COVID-19 is 3 (0–24)

days [13, 14]. Third, although both SARS-CoV-2 and SARS-CoV invade human cells through spike protein binding to the ACE2 receptor, in comparative structural analysis, the invasiveness and virulence of SARS-CoV-2 differ from those of SARS-CoV [15]. The pathological features of COVID-19 also display some differences to those of SARS and MERS [16].

As yet, no comprehensive comparison exists of the clinical characteristics and risk factors of these highly pathogenic CoVs, which is very important for clinical diagnosis and differential diagnosis as well as for improving the clinical understanding of these infectious agents. Current studies have reported the clinical characteristics of a large number of clinically diagnosed and confirmed cases of COVID-19. As the three most important CoV strains to emerge during the first decade of the 21st century, we sought to assess whether the SARS-CoV-2 genotype translates into a distinct clinical phenotype in humans, to provide insight into the pathogenesis of COVID-19. To this end, we performed a comparison of the risk factors, clinical presentation, and progression of patients hospitalized with SARS-CoV-2, MERS-CoV, and SARS-CoV infection.

Methods

Systematic literature review

We conducted a systematic literature review according to the WHO clinical guidelines and interim clinical guidelines for COVID-19, SARS, and MERS. We searched PubMed, Embase, CNKI, and Ovid/Medline on February 17, 2020, using the strategy "(((COVID-19) OR (SARS[Title])) OR (MERS)) OR (2019 novel coronavirus)". We limited our search to studies in English and Chinese language. We reviewed the identified publications regarding SARS-CoV, MERS-CoV, and COVID-19/SARS-CoV-2. In addition, the references of key articles were searched to identify additional eligible studies (Fig. 1).

Eligibility criteria

The eligibility of each article for inclusion was assessed according to the following criteria: 1) clinical research study reporting clinical characteristics; 2) all included patients meet the current SARS, MERS, or COVID-19 diagnostic standards; 3) more than 10 included patients; 4) the proportion of patients with clinical symptoms and laboratory test results is reported or could be extracted or estimated using reported data.

Data extraction

Studies were categorized according to clinical symptoms into a basic information group, underlying disease group, and admission for laboratory testing group. The results for all ranges were converted to quartiles, median, and standard deviation [17]. In cases with missing data for an included study, the corresponding author was contacted to request additional data.

Database

All patients with CoV infection reported in this manuscript were hospitalized. COVID-19 cases were diagnosed based on the WHO interim guidance [18]. Patients with laboratory-confirmed COVID-19 were all hospitalized in China between December 1, 2019 and January 29, 2020. The Chinese cases of SARS represent all hospitalized patients with laboratory-confirmed or clinically diagnosed SARS-CoV infection detected between December 22, 2002 and June 20, 2003. Greater Toronto Area SARS cases represent all hospitalized patients with laboratory-confirmed or clinically diagnosed SARS-CoV infection detected between March 7 and April 10, 2003. The Saudi Arabia MERS cases represent all hospitalized patients with laboratory-confirmed MERS-CoV infection detected between September 1, 2012 and June 1, 2016. Clinical and laboratory data were abstracted retrospectively from observational studies of SARS, COVID-19, and MERS cases, listed in supplementary table 1.

Risk factors for hospitalization and death

To assess the importance of putative risk factors of hospitalization for each CoV subtype, we estimated the relative risk of being hospitalized in individuals with and without risk factors. Data on the prevalence of each risk factor for the general Chinese population were used as denominators for the risk estimates and to weight (adjust) the overall relative risk estimates by age and sex. Data on age- and sex-specific population prevalence were available for chronic heart disease (CHD), chronic liver disease, chronic lung disease, chronic neurological disease, chronic renal disease, immunosuppression, diabetes, hypertension, smoking, and obesity. Age-specific but not sex-specific population prevalence data were available for asthma [19–22]. The age- and sex-stratified population prevalence of CHD (excluding isolated hypertension) was estimated from a study that recorded a prior history of hospitalization with coronary artery disease (history of hospitalization for myocardial infarction or a surgical history of coronary balloon angioplasty or coronary stent implantation or coronary artery bypass) [20]. We assumed that the age distribution of coronary artery disease is a valid proxy for the age distribution of CHD. Where surveys assessed disease prevalence only in older adults, we assumed that the prevalence was zero in those younger than the lower age limit of the survey. Because we were unable to source relevant baseline data for the Greater Toronto Area and Saudi Arabia, we assumed that the age distribution of chronic diseases is similar in the Chinese, Greater Toronto Area, and Saudi Arabia populations.

Statistical methods

We compared the characteristics of patients infected with different subtypes of CoV using Fisher's exact test or the $\chi 2$ test for comparing proportions and Wilcoxon signed-rank test for comparing medians of continuous variables. To evaluate the association between risk factors and the risk of hospitalization, Poisson regression was used to estimate the incidence rate ratios associated with each risk factor, adjusted for age and sex. Sample sizes were large and the distribution of the outcome similar to the normal distribution; the width of the interquartile range will be approximately 1.35 standard deviations. For ease of analysis, we treated all data reported as median as the mean and standard deviation [23].

Results

As of February 19, 2020, a total 74,280 laboratory-confirmed or clinically diagnosed cases of COVID-19 infection were officially recorded worldwide. Of these, we included 1406 patients who required hospitalization for medical reasons and laboratory testing in this study [2, 24–27]. Data were included for 4175 patients hospitalized with SARS-CoV infection (China = 4013; Greater Toronto Area = 144), and 512 patients hospitalized with MERS-CoV infection in Saudi Arabia (Fig. 1).

Our analysis showed that the proportion of men with COVID-19 was significantly higher than in those with SARS ($p < 0.001$) but lower than in patients with MERS ($p < 0.001$). The proportion of patients with COVID-19 who had any coexisting chronic medical conditions was significantly higher than in those with SARS ($p < 0.001$) but lower than this proportion in patients with MERS ($p < 0.001$). The prevalence of hypertension among patients with COVID-19 (17%) was higher than that of patients with SARS ($p < 0.001$). The prevalence of immunosuppression and malignancy was lower among patients with COVID-19 than among those with MERS who had CHD, chronic lung disease, chronic renal disease, and chronic neurological disease ($p < 0.001$). A history of smoking, male sex, any coexisting chronic medical condition and hypertension were found to be the most common risk factors for hospitalization with COVID-19 (Table 1).

We compared all hospitalization risk factor data with the average prevalence and sex ratio for COVID-19 in the Chinese population. We found that men were more susceptible than women to COVID-19 ($p < 0.001$). Patients with COVID-19 had a higher rate of any coexisting chronic medical conditions ($p < 0.001$) and a higher prevalence of heart-related diseases ($p < 0.001$). Rates of chronic kidney disease, chronic central nervous disease, hypertension, malignant tumor, and smoking history were all lower among patients with COVID-19 than those in the average Chinese population ($p < 0.001$), among which hypertension was the strongest risk factor for hospitalization ($p < 0.001$) (Table 2).

Signs and symptoms at hospital admission were compared for COVID-19 with SARS and COVID-19 with MERS. Fewer patients with COVID-19 exhibited fever, diarrhea, vomiting, nausea than those with the other two diseases ($p < 0.001$). Patients with COVID-19 were less likely to report myalgia and fatigue than those with SARS ($p < 0.001$). Cough symptoms were more prevalent among patients with COVID-19 than in those with SARS ($p < 0.001$), including for the subgroups productive cough, dry cough, and yellow sputum ($p < 0.001$). Only 1% of patients with COVID-19 had hemoptysis on admission, as compared with 2% with SARS and 17% with MERS ($p < 0.001$) (Table 3).

The values of hematological, liver, and renal function tests as well as inflammation markers on admission are shown in Table 5. The proportion of patients with COVID-19 who had elevated alanine transaminase (ALT) and aspartate transaminase (AST) was significantly lower than in those with SARS or MERS ($p < 0.001$). Fewer patients with COVID-19 had lymphopenia than did those with SARS, and elevated creatinine kinase was less prevalent in patients with COVID-19 than in patients with SARS ($p < 0.001$). However, thrombocytopenia, high lactate dehydrogenase (LDH), and elevated C-reactive protein (CRP) were more common in patients with COVID-19 than in those with SARS ($p < 0.001$).

Discussion

Herein, we report results of the first comparison of clinical characteristics and risk factors among hospitalized patients with SARS-CoV-2, MERS-CoV, or SARS-CoV infection. In our statistical analysis of the available published data, we determined that man sex and hypertension were the most common risk factors for COVID-19. Moreover, in comparison with patients with SARS or MERS, patients with COVID-19 showed lower prevalence of fever, diarrhea, vomiting, or nausea, but higher prevalence of cough symptoms thrombocytopenia, high LDH, and elevated CRP.

For all three CoVs investigated, men were found to be relatively more susceptible than women; we also identified a higher sex ratio in our study population than that in the general population of China, which may be a trait of CoV infection (Table 1). Surprisingly, in patients with COVID-19 who had high blood pressure, although the prevalence was higher than that among patients with SARS, it is still significantly lower the prevalence of hypertension in the national population of China. Among the CoV infection groups, the median age of patients with MERS is 57 years, and the prevalence of hypertension is significantly higher than the population average. However, the average age of patients with SARS or COVID-19 was younger (48 for COVID-19; 38 for SARS) (Tables 1 and 2), and these patients had a relatively low incidence of hypertension. Additionally, ACE2 has a strong affinity with the Ang II type 1 and type 2 receptors, regulating blood pressure, and the gene encodes a protein that is a functional receptor for the S glycoproteins of SARS-CoV-2 and SARS-CoV. Which may be another reason for the low incidence of hypertension in COVID-19.

Interestingly, we found that a smoking history was associated with lower risk of hospitalization among patients with COVID-19 than among the general Chinese population ($p < 0.001$). This finding may be owing to differences in the statistical methods used in the included studies, or owing to the small proportion of past smokers (only 3.1%) among women in our stud*y* [28]. However, a similar phenomenon has been reported for other viral agent*s* [29]; this finding may be worth further investigation.

Among common symptoms of fever and cough, the proportion of patients with COVID-19 who had fever was significantly lower than that in patients with SARS or MERS (Table 3). The prevalence of coexisting chronic diseases among patients with COVID-19 was not only higher than that among patients with SARS and MERS but was also higher relative to the average in the Chinese population. It believed that the disease history, such as low immunity [30], will also influence the common symptoms, relative to SARS and MERS have more higher rate of disease history (Table 1). Symptoms of the digestive tract are also less frequent in COVID-19, and the effect of SARS-CoV-2 on the digestive tract may be more limited than that of other viruses [14]. However, a recent study SARS-CoV-2 has been found in the feces of patients, indicating that fecal–oral transmission may be possible and replication in the digestive tract cannot be ruled out [31]. The probability of cough symptoms was 68% overall, and among the subgroups, dry cough symptoms was the most frequent (Table 3). The cause of frequent dry cough is inflammation of the lungs, even with a small amount of phlegm. It is possible that patients with dry cough have very thick

sputum that is difficult to discharge; therefore, patients in the hospital who have this symptom should be closely monitored.

In patients with COVID-19, prolific thrombocytopenia, hemoptysis, elevated LDH, and elevated CRP were common (Table 4). Decreased lymphocytes and elevated AST, ALT, and CK are common in patients with SARS and are associated with a more severe prognosis. In one study, elevated LDH was found to be a risk factor for acute respiratory distress syndrome (ARDS) in patients with SARS [32]. In patients hospitalized for SARS, a lower absolute lymphocyte count was associated with poorer prognosis [33]. Hematological and serum chemical abnormalities indicate that hospitalized patients with COVID-19 have serious systemic disease [34]. It is yet to be determined whether this is the result of severe pneumonia and poor tissue oxygenation (such as in SARS) or an excessive inflammatory response [35]. It is known that these indexes exist in patients with COVID-19; however, further research is needed to confirm the correlation with severity of disease and whether these affect the course of this disease.

Certainly, there are some limitations in this study. First, this was a meta-analysis and there were some missing data. Second, COVID-19 is a newly identified infectious disease, the understanding of which is still evolving; some clinical data and outcomes may be updated in the future.

Conclusion

This comparative analysis showed that patients hospitalized with SARS-CoV-2 infection share some risk factors with those hospitalized for SARS-CoV and MERS-CoV infection. However, we identified differences in the clinical profiles of infection with these CoVs. Generally, clinical signs and symptoms of SARS-CoV-2 infection were less severe than those of SARS-CoV and MERS-CoV infection, which may be the cause of low mortality owing to COVID-19. However, male sex, smoking history, and hypertension were identified as the most common risk factors for hospitalization owing to COVID-19 in this study. Greater attention is needed for patients with these risk factors in clinical practice, to improve clinical treatment and control the rate of SARS-CoV-2 infection.

Abbreviations

MERS: Middle East Respiratory Syndrome Coronavirus; SARS: Severe Acute Respiratory Syndrome; CoV: Coronavirus; CFR: Case Fatality Ratio; CHD: Chronic Heart Disease; LDH: Lactate Dehydrogenase; ACE2: Angiotensin Convetting Enzyme 2; CK: Creatine Kinase.

Declarations

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

Not applicable.

Availability of data and material:

The data that support the findings of this study are available from [PubMed, Embase, CNKI, and Ovid/Medline] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [PubMed, Embase, CNKI, and Ovid/Medline].

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Competing interests:

The authors report no conflicts of interest.

Authors' contributions:

All authors fulfill the contribution requirements as per the International Committee of Medical Journal Editors' role of authors and contributors' guidelines. All authors conceptualized and designed the study and critically reviewed and revised the manuscript. Z.T.L and X.D.W carried out the analyses and wrote the initial manuscript. G.S.S extracted data and carried out analyses. Z.T.L and F.Y oversaw manuscript development.

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Tables

Table 1. Characteristics of patients hospitalized with COVID-19, SARS, and MERS

Characteristic	COVID-2019	SARS	P Value	MERS	P Value
Age, y, median (range)	Mean□48.7258 SD□6.0324 n=1406	Mean □ 37.7274 SD □ 12.3664 n=1532	0.439	Mean□57.6846 SD□10.513 n=512	0.439
Interval from onset, admission days (IQR)	Mean=3.4961 SD=3.9383 n=1278	0/0	N/A	Mean=5 SD=0.833 n=330	1
Male sex	812/1377(59%)	965/2533(38%)	□0.001	352/512(69%)	□0.001
Any coexisting chronic medical conditions	432/1406(31%)	329/1488(22%)	□0.001	45/47(96%)	□0.001
Chronic heart disease	93/1377(7%)	33/471(7%)	0.851	191/512(37%)	□0.001
Chronic lung disease	19/1406(1%)	6/351(2%)	0.612	71/512(14%)	□0.001
Chronic renal disease	26/1377(2%)	5/273(2%)	0.95	154/512(30%)	□0.001
Chronic liver disease	40/1365(3%)	9/237(4%)	0.474	28/465(6%)	0.002
Chronic neurological disease	29/1336(2%)	0/108(0%)	0.122	36/330(11%)	□0.001
Diabetes	120/1406(9%)	54/724(7%)	0.39	271/512(53%)	□0.001
Asthma	0/0	1/14(7%)	N/A	18/330(5%)	N/A
Immune compromise	2/1099(0%)	1/53(2%)	0.17	24/377(6%)	□0.001
Hypertension	221/1307(17%)	29/582(5%)	□0.001	16/47(34%)	0.002
Malignancy	22/1307(2%)	16/436(4%)	0.14	36/424(8%)	□0.001
Pregnancy	1/29(3%)	1/96(1%)	0.365	0/0	N/A
Smoking history	160/1128(14%)	0/14(0%)	0.129	11/47(23%)	0.079

Abbreviations: COVID-19, coronavirus disease 2019; SARS, severe acute respiratory syndrome-associated coronavirus; MERS, Middle East respiratory syndrome-associated coronavirus.

Table 2. Age- and sex-adjusted risk factors for hospitalization

Characteristic	COVID-2019	China	P Value
Male sex	812/1377(59%)	49%	0.001
Any coexisting chronic medical conditions	432/1406(31%)	25%	0.001
Chronic heart disease (assume zero prevalence aged <18 y)	93/1377(7%)	1%	0.001
Chronic lung disease	19/1406(1%)		
Chronic renal disease(assume zero prevalence aged <18 y)	26/1377(2%)	13%	0.001
Chronic liver disease	40/1365(3%)		
Chronic neurological disease	29/1336(2%)		
Diabetes	120/1406(9%)	10%	0.325
Hypertension(assume zero prevalence aged <20 y)	221/1307(17%)	25%	0.001
Malignancy	22/1307(2%)	0%	0.001
Pregnancy	1/29(3%)		
Smoking history	160/1128(14%)	27%	0.001

Abbreviations: COVID-19, coronavirus disease 2019; SARS, severe acute respiratory syndrome-associated coronavirus; MERS, Middle East respiratory syndrome-associated coronavirus.

Table 3. Signs and symptoms on admission

tic	COVID-2019	SARS	P Value	MERS	P Value
≥37.8)	731/1377(53%)	3155/3223(98%)	<0.001	370/512(72%)	<0.001
	959/1406(68%)	1874/3367(56%)	<0.001	266/377(71%)	0.382
cough	582/1406(41%)	859/3040(28%)	<0.001	17/47(36%)	0.474
	571/1377(41%)	569/2764(21%)	<0.001	22/47(47%)	0.465
um	48/276(17%)	5/106(5%)	0.001	0/0	N/A
	12/1377(1%)	6/272(2%)	0.053	8/47(17%)	<0.001
	252/1406(18%)	1404/2757(51%)	<0.001	79/377(21%)	0.179
	533/1377(39%)	602/1118(54%)	<0.001	114/330(35%)	0.162
f breath	317/1405(23%)	305/1512(20%)	0.115	34/47(72%)	<0.001
tinal symptoms	78/1377(6%)	21/868(2%)	<0.001	195/512(38%)	<0.001
	62/1406(4%)	528/2186(24%)	<0.001	50/377(13%)	<0.001
	6/237(3%)	59/523(11%)	<0.001	68/377(18%)	<0.001
	15/237(6%)	813/2600(31%)	<0.001	68/377(18%)	<0.001
vous system symptoms	34/278(12%)	0/0	N/A	0/0	N/A

Abbreviations: COVID-19, coronavirus disease 2019; SARS, severe acute respiratory syndrome-associated coronavirus; MERS, Middle East respiratory syndrome-associated coronavirus.

Table 4. Laboratory results on admission

eristic	COVID-2019	SARS	P Value	MERS	P Value
ell count	Mean=4.7265	Mean=5.3444	1	Mean=6.8645	0.121
	SD=0.575	SD=1.8319		SD=1.3215	
	n=1278	n=641		n=465	
cyte count	Mean=0.972	Mean=3.4658	1	0/0	N/A
	SD=0.1973	SD=5.2006			
	n=1278	n=479			
phil count	Mean=4.0072	Mean=2.6316	0.439	0/0	N/A
	SD=1.2314	SD=2.1397			
	n=278	n=563			
count	Mean=167.3318	Mean=162.7621	1	Mean=176.1774	1
	SD=12.3628	SD=48.867		SD=28.3151	
	n=1278	n=543		n=465	
	Mean=33.9964	Mean=36.7	1	Mean=61.4839	0.121
	SD=6.408	SD=10		SD=13.9459	
	n=278	n=68		n=465	
	Mean=29.036	Mean=27.9671	1	Mean=39.2581	0.439
	SD=6.4906	SD=36.4892		SD=10.3953	
	n=278	n=243		n=465	
reatinine	Mean=72.5039	Mean=43.164	1	Mean=111.8065	0.121
	SD=5.2549	SD=49.97		SD=32.996	
	n=179	n=371		n=465	
	Mean=95.4802	Mean=49.5151	1	0/0	N/A
	SD=36.8267	SD=131.0857			
	n=278	n=292			
	Mean=291.3957	Mean=308.1137	1	0/0	N/A
	SD=49.3863	SD=115.0849			
	n=278	n=387			
enia	372/1146(32%)	387/1267(31%)	0.311	0/0	N/A
penia	81/169(48%)	305/390(78%)	0.001	0/0	N/A
philia	38/99(38%)	0/0	N/A	0/0	N/A
ocytopenia	329/1008(33%)	150/979(15%)	0.001	0/0	N/A

↑ AST	203/885(23%)	182/385(47%)	<0.001	203/245(83%)	<0.001
↑ ALT	213/910(23%)	234/686(34%)	<0.001	107/275(39%)	<0.001
↑ CK	116/796(15%)	311/1557(20%)	0.001	0/0	N/A
↑ CRP	508/822(62%)	97/190(51%)	0.006	0/0	N/A
↑ LDH	401/843(48%)	371/1499(25%)	<0.001	0/0	N/A

Abbreviations: COVID-19, coronavirus disease 2019; SARS, severe acute respiratory syndrome-associated coronavirus; MERS, Middle East respiratory syndrome-associated coronavirus. AST, aspartate transaminase; ALT, alanine transaminase; CK, creatinine kinase; CRP, C-reactive protein; LDH, lactate dehydrogenase.

Table 5, mentioned on page 9, was omitted by the authors in this version of the paper.

Figures

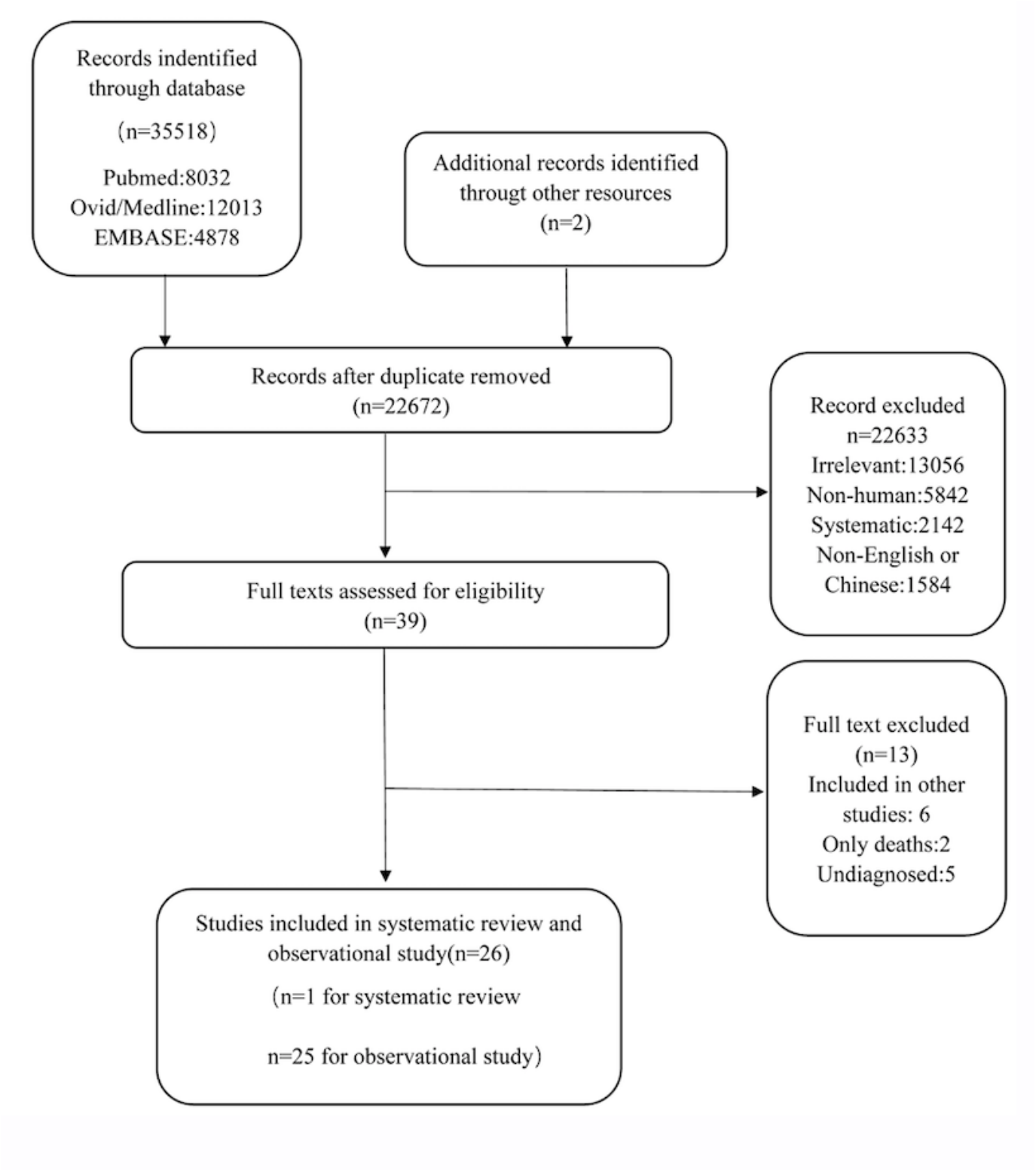

Figure 1

Flow chart showing the process of screening the published data.

Supplementary Files

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- Supplementarytable1.pdf