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REVIEW ARTICLE

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Ferritin in the coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis

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Abstract

Objective: The coronavirus disease 2019 (COVID-19) has rapidly developed into a pandemic. Increased levels of ferritin due to cytokine storm and secondary hemophagocytic lymphohistiocytosis were found in severe COVID-19 patients. Therefore, the aim of this study was to determine the role of ferritin in COVID-19.

Methods: Studies investigating ferritin in COVID-19 were collected from PubMed, EMBASE, CNKI, SinoMed, and WANFANG. A meta-analysis was performed to compare the ferritin level between different patient groups: non-survivors versus survivors; more severe versus less severe; with comorbidity versus without comorbidity; ICU versus non-ICU; with mechanical ventilation versus without mechanical ventilation.

Results: A total of 52 records involving 10 614 COVID-19-confirmed patients between December 25, 2019, and June 1, 2020, were included in this meta-analysis, and 18 studies were included in the qualitative synthesis. The ferritin level was significantly increased in severe patients compared with the level in non-severe patients [WMD 397.77 (95% CI 306.51-489.02), $P < .001$]. Non-survivors had a significantly higher ferritin level compared with the one in survivors [WMD 677.17 (95% CI 391.01-963.33), $P < .001$]. Patients with one or more comorbidities including diabetes, thrombotic complication, and cancer had significantly higher levels of ferritin than those without ($P < .01$). Severe acute liver injury was significantly associated with high levels of ferritin, and its level was associated with intensive supportive care, including ICU transfer and mechanical ventilation.

Conclusions: Ferritin was associated with poor prognosis and could predict the worsening of COVID-19 patients.

KEYWORDS

comorbidity, COVID-19, diagnosis, ferritin, mortality, severity

Linlin Cheng and Haolong Li contributed equally to this work.

1 | INTRODUCTION

Since December 2019, the coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has rapidly developed into a global outbreak characterized by a human-to-human transmission.[1,2] On March 11, 2020, WHO declared the COVID-19 a pandemic. It has caused a total of 30 675 675 confirmed cases, including 954 417 deaths as of September 20, 2020.[3] Patients with comorbidities such as diabetes, cardiovascular disease, underlying respiratory diseases, and cancer are at high risk of severe complications and even death. This is a global crisis that requires the joint efforts of all mankind to fight it.

The cytokine storm is an uncontrolled and dysfunctional immune response in the immunopathogenic mechanism of COVID-19 similar to the one in severe influenza; inflammatory cytokines including TNF-α, IL-6, IL-12, and IL-8 are released in a massive amount during the disease progression, causing potential acute respiratory distress syndrome (ARDS) and systemic organ failure.[4-6] Evidence shows that the levels of serum ferritin, d-dimer, lactate dehydrogenase, and IL-6 are increased during the worsening of the disease, providing an indication of the risk of mortality.[6]

Hyperferritinemia caused by the excessive inflammation due to the infection is associated with the admission to the intensive care unit and high mortality, and represents an indication to recognize high-risk patients to guide the therapeutic intervention to control inflammation.[7-9] Serum ferritin, a feature of hemophagocytic lymphohistiocytosis, which is a known complication of viral infection, is closely related to poor recovery of COVID-19 patients, and those with impaired lung lesion are more likely to have increased ferritin levels.[6,10,11] However, these studies were performed in a relatively small sample size and/or in a single center. Thus, as a pro-inflammatory factor in the uncontrolled cytokine storm, the predictive role of the ferritin level in the risk of poor outcome in COVID-19 patients requires further verification.

The laboratory tests combined with the clinical evaluation can allow a rapid assessment of the patient's condition to guide clinicians in finding the optimal approach and priority in these COVID-19 patients. Serum ferritin is particularly interesting due to its potential diagnostic and prognostic role. In this study, the current studies on COVID-19 were comprehensively investigated to determine the potential relationship of ferritin with severe condition, mortality, and other critical clinical features of COVID-19 patients.

2 | METHODS

2.1 | Study design and literature search

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis Diagnostic Test Accuracy (PRISMA-DTA) guideline[12] and Meta-analysis of Observational Studies in Epidemiology (MOOSE)[13] were followed to create this review. Seven databases such as PubMed, EMBASE, CNKI, SinoMed, and WANFANG were used to comprehensively search COVID-19-related studies. The searching items in all "fields" were the following: (coronavirus) OR (pneumonia) OR (nCoV) OR (HCoV) OR (SARS-CoV-2) OR (COVID) OR (NCP) AND ferritin. No restrictions were imposed regarding the language, region of the investigation, or ethnicity of the study population. The reference list of the included articles was also examined. The last retrieval time was August 16, 2020.

2.2 | Selection criteria

Eligible studies were those that investigated ferritin and its clinical relevance in patients diagnosed with COVID-19. The exclusion criteria were as follows: (1) review articles; (2) case reports; (3) studies without available laboratory data; (4) pre-printed articles without peer review; (5) incorrect study design or simple data presentation; and (6) patients age no more than 18 years. Two investigators independently performed the literature search, screening, full-text review, and the study quality assessment using the Newcastle-Ottawa Scale (NOS). Inter-researcher disagreement was resolved by consensus, or by the discussion with a third investigator.

2.3 | Data extraction

Two independent investigators performed the data extraction, including date of publication, first author's name, region of the investigation, number of included cases, age (statistical significance), gender (statistical significance), ferritin level in the different groups (non-survivors vs. survivors; more severe vs. less severe; with comorbidity vs. without comorbidity; subjected to a certain treatment vs. without being subjected to a certain treatment), and diagnosis guideline. Primary data were extracted from the article text or tables. For further meta-analysis, categorical variables (such as gender, region of the investigation, comorbidities, symptoms, treatment, or endpoint events) are treated as dichotomous variables, while for continuous variables (such as age and ferritin results), median (interquartile range, IQR) or median (range) was converted to mean ± SD for meta-analysis according to Wan et al[14]. Any disagreement was resolved through discussion.

2.4 | Statistical analysis

The meta-analysis was performed by Stata 12.0. The weighted mean difference (WMD) was used as the effect measure in the comparison between different patient groups. The random effects model was chosen for analysis, since it tends to generalize findings beyond the included studies by assuming that the selected studies are random samples from a larger population.[15] Heterogeneity among studies was evaluated using the Cochran's Q-statistic and I^2-statistic. *P*-values > .10 or $I^2 > 50\%$ were considered as indicating a significant heterogeneity. The sensitivity analysis was performed by leave-one-out analysis to evaluate the stability of the results. The random

effects meta-regression was performed to explore the source of heterogeneity. Egger's test and funnel plot were used to examine the publication bias of the analysis according to Sterne et al.[16]

3 | RESULTS

3.1 | Literature search and characteristics of the included studies

A total of 777 records were collected by the databases and manual searching. After the exclusion of the duplicates, review articles, case reports, pre-printed versions without peer-review, and irrelevant studies by title or abstract screening, 187 studies remained for full-text review; 52 studies[6,17-67] were finally included into the meta-analysis, and 18 studies were included in the qualitative synthesis (Figure 1). A total of 52 records involving 10 614 COVID-19 patients confirmed between December 25, 2019, and June 1, 2020, were included. The repetition of patients from the same hospital was examined during the same period. Most of the selected studies (29/52) were performed in China.[6,17-25,27-32,35-37,50,59-67] Ten studies were performed in multicenters.[6,17,23,34,45,49,57,58,60,64] Among the included studies, 17 compared the ferritin level between groups with different severity of COVID-19[18-22,34,35,37-39,44,50,53,56,61,64,65] and 18 compared its level between non-survivors and survivors.[6,17,23,24,26-29,40-42,45,46,52,55,58,63,66] The characteristics of all studies included in this meta-analysis are listed in Table 1. The study quality performed by the NOS is shown in Table 2. All studies were of high quality with a score from 7 to 9.

3.2 | Association of ferritin with the severity of COVID-19

The forest plot showed that the ferritin level was significantly higher in more severe patients than that in less severe patients [WMD

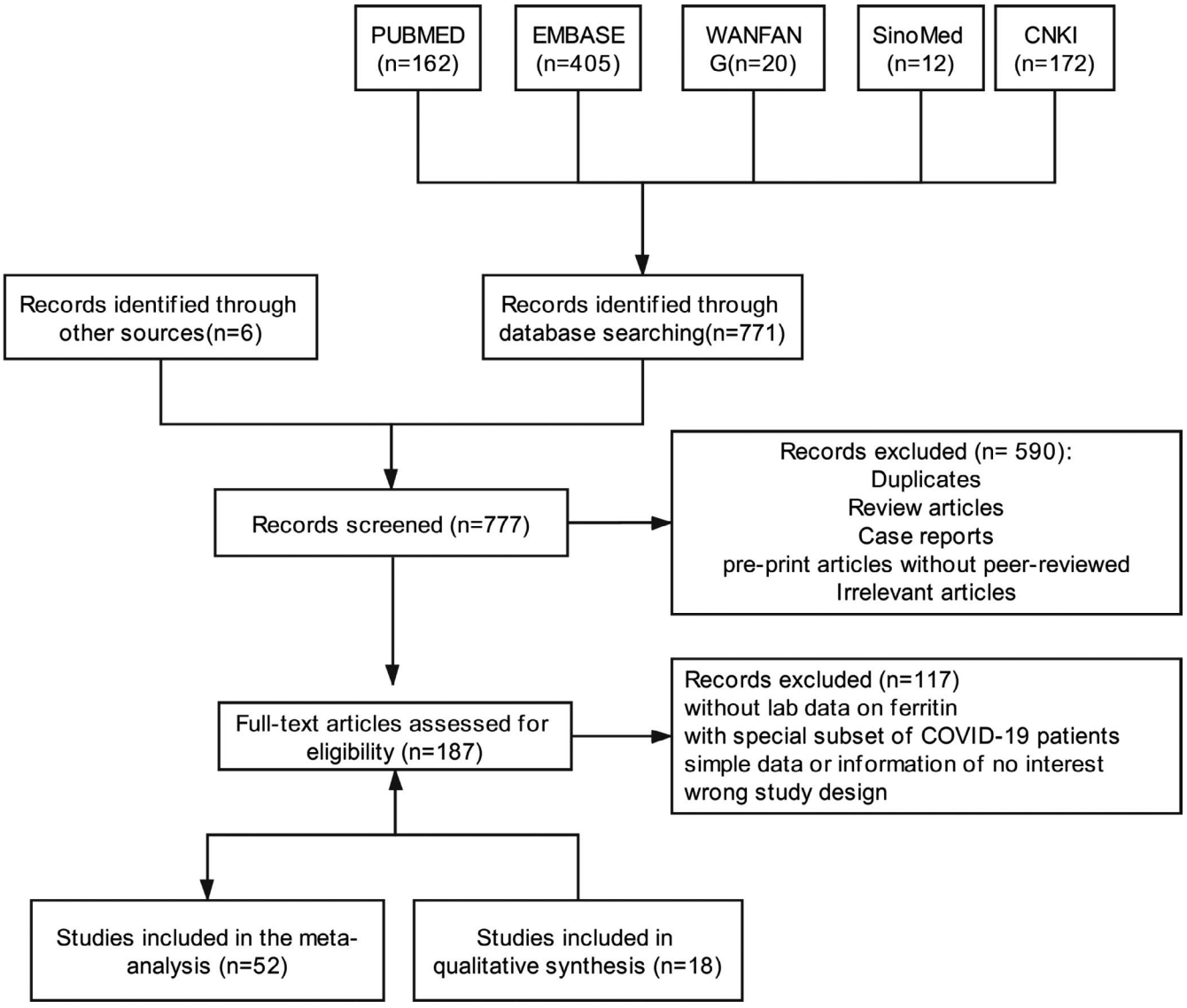

FIGURE 1 Flowchart of the literature selection

TABLE 1 Characteristics of the studies included in the meta-analysis

Studies	Cases	Age, y, mean ± SD/median (IQR)	Male (%)	Group comparison	Country
Akshay Shah et al	30	57.0 (52.0-64.0)	17 (57.0%)	Severe patients versus non-severe patients	UK
Ali A. Ghweil et al	66	58.7 ± 10.6	48 (72.7%)	Severe patients versus non-severe patients	Egypt
Anne Lohse et al	34	75.1 ± 11.1	24 (70.6%)	Non-survivors versus survivors	France
C. Sieiro Santos et al	38	74.8 ± 6.3	18 (47.4%)	Non-survivors versus survivors	Spain
Christopher M. Petrilli et al	2729	63.0 (51.0-74.0)	1672 (61.3%)	Severe patients versus non-severe patients	USA
David J. Pinato et al	204	69.3 ± 13.0	127 (62.3%)	Non-survivors versus survivors	UK
Edgar Ortiz-Brizuela et al	140	50.9 ± 19.0	85 (60.7%)	ICU versus non-ICU	Mexico
Edward Itelman et al	162	52.0 ± 20.0	105 (64.8%)	Severe patients versus non-severe patients	Israel
Elena Aloisio et al	427	61.0 (50.0-73.0)	293 (69.0%)	Non-survivors versus survivors	Italy
Elena Aloisio et al	427	61.0 (50.0-73.0)	293 (69.0%)	ICU versus non-ICU	Italy
Elİf Tanriverdİ et al	83	50.7 ± 13.8	60 (72.2%)	Non-survivors versus survivors	Turkey
Francisco Hernández-Fernández et al	40	67.5 ± 12.2	31 (77.5%)	Cerebral ischemia versus no cerebral ischemia	Spain
Gennaro Giustino et al	112	57.4 ± 18.1	76 (67.9%)	CVD versus non-CVD	USA
Graziella Bonetti et al	144	68.8 ± 16.2	96 (66.7%)	Non-survivors versus survivors	Italy
Hanny Al-Samkari et al	400	65.0 ± 19.0	228 (57.0%)	Thrombotic complication versus no complication.	USA
Hanny Al-Samkari et al	400	65.0 ± 19.0	228 (57.0%)	Bleeding complication versus no complication	USA
Issam Koleilat et al	135	62.5 ± 14.8	72 (53.3%)	DVT versus no DVT	USA
Laguna-Goya Rocio et al	501	52.0 (44.0-60.0)	317 (63.3%)	Non-survivors versus survivors	Spain
Massimo Cugno et al	31	59.0 ± 13.5	21 (67.7%)	Severe patients versus non-severe patients	Italy
Mathieu Artifoni et al	71	64.0 (46.0-75.0)	43 (60.6%)	VTE versus no VTE	France
Natalia Chamorro-Pareja et al	50	52.6 ± 20.5	32 (64.0%)	Non-survivors versus survivors	USA
Rahmet Güner et al	222	50.6 ± 16.5	132 (59.5%)	Severe patients versus non-severe patients	Turkey
Rosa Bellmann-Weiler et al	259	66.8 ± 19.4	157 (60.6%)	No anemia versus anemia	Austria
Şiran Keske et al	43	62.3 ± 15.3	31 (72.0%)	Non-survivors versus survivors	Turkey
Tobias Herold et al	40	53.5 ± 14.4	29 (72.0%)	Mechanical ventilation versus no mechanical ventilation (evaluation cohort)	Germany
Tobias Herold et al	49	57.5 ± 14.8	33 (67.0%)	Mechanical ventilation versus no mechanical ventilation (validation cohort)	Germany
Chaomin Wu et al	201	51.0 (43.0-60.0)	128 (63.7%)	with ARDS versus without ARDS	China
Chaomin Wu et al	84	58.5 (50.0-69.0)	60 (71.4%)	Non-survivors versus survivors (with ARDS)	China

(Continues)

TABLE 1 (Continued)

Studies	Cases	Age, y, mean ± SD/median (IQR)	Male (%)	Group comparison	Country
Chuan Qin et al	452	58.0 (47.0-67.0)	235 (52.0%)	Severe patients versus non-severe patients	China
Fei Zhou et al	191	56.0 (46.0-67.0)	119 (62.0%)	Non-survivors versus survivors	China
Fen Wang et al	115	62.0 ± 9.3	56 (94.9%)	Diabetes versus non-diabetes	China
Feng Wang et al	65	57.1 ± 13.0	37 (57.0%)	Severe patients versus non-severe patients	China
Feng Wang et al	28	68.6 ± 9.0	21 (75.0%)	ICU versus non-ICU	China
Guang Chen et al	21	56.0 (50.0-65.0)	17 (81.0%)	Severe patients versus non-severe patients	China
Hang Yang et al	94	67.2 ± 11.1	45 (47.9%)	Non-survivors versus survivors	China
Hui Song et al	84	66.5 ± 12.2	56 (66.7%)	Non-survivors versus survivors	China
Huihuang Huang et al	64	47.8 ± 18.5	32 (50.0%)	Severe patients versus non-severe patients	China
Jihua Shi et al	46	62.5 (50.5, 68.5)	31 (57.4%)	Severe patients versus non-severe patients	China
Jing Liu et al	40	48.7 ± 13.9	15 (37.5%)	Severe patients versus non-severe patients	China
Kebin Cheng et al	463	51.0 (43.0, 60.0)	244 (52.7%)	Severe patients versus non-severe patients	China
Lu Qin et al	233	56.0 ± 1.0	100 (42.9%)	Without comorbidity versus without comorbidity	China
Lu Qin et al	233	56.0 ± 17.0	100 (42.9%)	Male versus female	China
Mingyue Li et al	83	45.7 ± 22.6	34 (41.0%)	CVD versus non-CVD	China
Qiongfang Zha et al	85	54.2 ± 16.0	57 (67.1%)	Severe patients versus non-severe patients	China
Qiurong Ruan et al	150	56.5 ± 39.4	102 (68.0%)	Non-survivors versus survivors	China
Shengping Liu et al	255	64.0 (24.0-92.0)	136 (53.3%)	ICU versus non-ICU	China
Songjiang Huang et al	225	59.0 (45.0-68.0)	124 (55.1%)	Hypertension versus non-hypertension	China
Tao Chen et al	274	62.0 (44.0-70.0)	171 (62.0%)	Non-survivors versus survivors	China
Tao Liu et al	80	54.5 ± 12.4	34 (42.5%)	Severe patients versus non-severe patients	China
Weina Guo et al	50	41.0 (32.0-60.0)	21 (42.0%)	Diabetes versus non-diabetes (without other comorbidities)	China
Weina Guo et al	174	59.0 (49.0-67.0)	76 (43.7%)	Diabetes versus non-diabetes	China
Xia Xu et al	88	57.1 ± 15.4	36 (40.9%)	Severe patients versus non-severe patients	China
Xue Wang et al	113	58.6 ± 15.9	68 (60.2%)	Non-survivors versus survivors	China
Yang Zhang et al	145	62.0 ± 4.5	74 (51.0%)	Diabetes versus non-diabetes	China
Yifan Meng et al	436	58.9 ± 16.0	244 (60.0%)	Cancer patients versus non-cancer patients	China
Yongli Yan et al	48	69.4 ± 9.9	33 (68.8%)	Non-survivors versus survivors (all severe patients)	China
Yongli Yan et al	193	62 ± 17.9	114 (59.1%)	Diabetes versus non-diabetes (all severe patients)	China
Zhaohua Wang et al	59	67.4 ± 11.3	38 (64.4%)	Non-survivors versus survivors	China
Zhi Lin et al	147	46.3 ± 12.4	71 (48.3%)	Severe patients versus non-severe patients	China

Abbreviations: ARDS, acute respiratory distress syndrome; CVD, cardiovascular disease; DVT, deep venous thrombosis; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation; VTE, venous thromboembolism.

TABLE 2 Quality assessment of the included studies according to the Newcastle-Ottawa Scale (NOS)

NOS item/Study ID	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of both groups for age
Akshay Shah et al	☆	☆	☆	☆	☆
Ali A. Ghweil et al	☆	☆	☆	☆	
Anne Lohse et al	☆	☆	☆	☆	☆
C. Sieiro Santos et al	☆	☆	☆	☆	
Christopher M. Petrilli et al	☆	☆	☆	☆	
David J. Pinato et al	☆	☆	☆	☆	
Edgar Ortiz-Brizuela et al	☆	☆	☆	☆	☆
Edward Itelman et al	☆	☆	☆	☆	
Elena Aloisio et al	☆	☆	☆	☆	☆
Elİf Tanriverdİ et al	☆	☆	☆	☆	
Francisco Hernández-Fernández et al	☆	☆	☆	☆	☆
Gennaro Giustino et al	☆	☆	☆	☆	☆
Graziella Bonetti et al	☆	☆	☆	☆	
Hanny Al-Samkari et al	☆	☆	☆	☆	
Issam Koleilat et al	☆	☆	☆	☆	☆
Laguna-Goya Rocio et al	☆	☆	☆	☆	
Massimo Cugno et al	☆		☆	☆	
Mathieu Artifoni et al	☆	☆	☆	☆	☆
Natalia Chamorro-Pareja et al	☆	☆	☆	☆	
Rahmet Güner et al	☆	☆	☆	☆	
Rosa Bellmann-Weiler et al	☆	☆	☆	☆	
Şiran Keske et al	☆	☆	☆	☆	
Tobias Herold et al	☆	☆	☆	☆	☆
Chaomin Wu et al	☆	☆	☆	☆	
Chuan Qin et al	☆	☆	☆	☆	
Fei Zhou et al	☆	☆	☆	☆	
Fen Wang et al	☆	☆	☆	☆	
Feng Wang et al	☆	☆	☆	☆	
Feng Wang et al	☆	☆	☆	☆	☆
Guang Chen et al	☆	☆	☆	☆	
Hang Yang et al	☆	☆	☆	☆	☆
Hui Song et al	☆	☆	☆	☆	☆
Huihuang Huang et al	☆	☆	☆	☆	
Jihua Shi et al	☆	☆	☆	☆	☆
Jing Liu et al	☆	☆	☆	☆	
Kebin Cheng et al	☆	☆	☆	☆	
Lu Qin et al	☆	☆	☆	☆	
Mingyue Li et al	☆	☆	☆	☆	
Qiongfang Zha et al	☆	☆	☆	☆	☆
Qiurong Ruan et al	☆		☆	☆	
Shengping Liu et al	☆	☆	☆	☆	☆
Songjiang Huang et al	☆		☆	☆	
Tao Chen et al	☆	☆	☆	☆	

Comparability of both groups for gender	Ascertainment of diagnosis	Same method of ascertainment for cases and controls	Non-response rate	Total score
	☆	☆	☆	8
☆	☆	☆	☆	8
	☆	☆	☆	8
☆	☆	☆	☆	8
	☆	☆	☆	7
	☆	☆	☆	7
☆	☆	☆	☆	9
	☆	☆	☆	7
	☆	☆	☆	8
	☆	☆	☆	7
☆	☆	☆	☆	9
☆	☆	☆	☆	9
☆	☆	☆	☆	8
	☆	☆	☆	7
☆	☆	☆	☆	9
☆	☆	☆	☆	8
	☆	☆	☆	6
☆	☆	☆	☆	9
	☆	☆	☆	7
☆	☆	☆	☆	8
☆	☆	☆	☆	8
☆	☆	☆	☆	8
	☆	☆	☆	8
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	☆	☆	☆	7
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☆	☆	☆	☆	9
☆	☆	☆	☆	8
☆	☆	☆	☆	8
	☆	☆	☆	7
☆	☆	☆	☆	8
☆	☆	☆	☆	9
☆	☆	☆	☆	7
	☆	☆	☆	8
☆	☆	☆	☆	7
	☆	☆	☆	7

(Continues)

TABLE 2 (Continued)

NOS item/Study ID	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of both groups for age
Tao Liu et al	☆	☆	☆	☆	
Weina Guo et al	☆	☆	☆	☆	
Xia Xu et al	☆	☆	☆	☆	
Xue Wang et al	☆	☆	☆	☆	
Yang Zhang et al	☆	☆	☆	☆	
Yifan Meng et al	☆	☆	☆	☆	☆
Yongli Yan et al	☆	☆	☆	☆	☆
Zhaohua Wang et al	☆	☆	☆	☆	
Zhi Lin et al	☆		☆	☆	

Note: ☆ was assigned when the respective information was available.

397.77 (95% CI 306.51-489.02), $P < .001$] (Figure 2). Heterogeneity was observed in the meta-analysis ($I^2 = 80.6\%$, $P < .001$). However, the sensitivity analysis showed the stability of the pooled results after the leave-one-out analysis (Figure 3). The meta-regression also did not demonstrate any significant effect of age, gender, and case number on the polled results in the meta-analysis. The funnel plot and the Egger's test revealed the presence of publication bias ($P = .007$) (Supplementary Figure 1).

Lu et al reported that COVID-19 patients with high levels of ferritin have greater proportions of severe and deceased cases ($P = .0016$).[30] Similarly, Sun et al revealed that severe patients and discharged patients have greater proportions of increased level of ferritin than non-severe patients and hospitalized patients (100% vs. 50%, 92.3% vs. 37.9% respectively, $P < .001$) and suggested that serum ferritin is a potential risk factor of poor prognosis in COVID-19 patients.[68] In the study by Hou et al, ferritin was selected as a prediction marker of severe COVID-19 by multivariable logistic regression analysis [odds ratio (OR) = 1.0006 (97.5% CI 1.0001-1.0010), $P = .206$] and the area under the curve (AUC) to differentiate critical from mild patients was 0.812.[69]

3.3 | Association of ferritin with the mortality of COVID-19

The forest plot showed that the non-survivors with COVID-19 had a significantly higher level of ferritin compared with the COVID-19 survivors [WMD 677.17 (95% CI 391.01-963.33), $P < .001$] (Figure 4). Heterogeneity was observed in the meta-analysis ($I^2 = 89.0\%$, $P < .001$). However, the sensitivity analysis showed the stability of the pooled results after the leave-one-out analysis (Figure 5). The meta-regression showed no significant effect of age, gender, and case number on the polled results in the meta-analysis. The study by Yan et al revealed higher WMD in severe COVID-19 patients when comparing non-survivors and survivors (Figure 4). However, the ferritin level did not reveal any significant difference in patients with ARDS after stratification by mortality in the study of Wu et al (Figure 4). The funnel plot and the Egger's test showed no publication bias ($P = .652$) (Supplementary Figure 2).

Cecconi et al also revealed that ferritin can aid the early identification and management of patients at risk of clinical deterioration leading to ICU transfer or death in hospitalized COVID-19 patients.[70] Notably, the changes of ferritin levels in the COVID-19 patients are not only higher in non-survivors than in survivors, but also increase with the worsening of the disease.[6] Similarly, a biphasic changing pattern of ferritin was observed in COVID-19 patients subjected to solid organ transplant between ICU and non-ICU patients. Indeed, ferritin levels increased during the stay, with a later peak at day 19 in the ICU patients, who have higher rate of mortality (36% vs. 5%) and co-infection (36% vs. 15%) than non-ICU patients. However, no significant changes of ferritin levels were observed in COVID-19 patients during ICU stay by Bolondi et al.[71]

3.4 | Association of ferritin with comorbidity and gender

Studies that determined the association of the ferritin level with baseline conditions (comorbidity, gender) were included in this meta-analysis (Figure 6). Patients with one or more comorbidities including diabetes, thromboembolic events, and cancer had significantly higher levels of ferritin than those without ($P < .01$, Figure 6). In accordance with the meta-analysis of severe versus non-severe, when comparing patients with diabetes and those without diabetes, the study by Yan et al revealed relatively higher WMD of ferritin levels in severe patients than that found in other studies [WMD 670.87 (95% CI 262.32-1079.41)] (Figure 6). In addition, Wang et al revealed a positive correlation between levels of ferritin and glycosylated hemoglobin (HbA1c) ($r = .24$, $P = .01$).[72] No significant differences in ferritin levels were observed within COVID-19 patients who had cardiovascular disease, anemia,

Comparability of both groups for gender	Ascertainment of diagnosis	Same method of ascertainment for cases and controls	Non-response rate	Total score
	☆	☆	☆	7
☆	☆	☆	☆	8
	☆	☆	☆	7
	☆	☆	☆	7
☆	☆	☆	☆	8
☆	☆	☆	☆	9
	☆	☆	☆	8
☆	☆	☆	☆	8
☆	☆	☆	☆	7

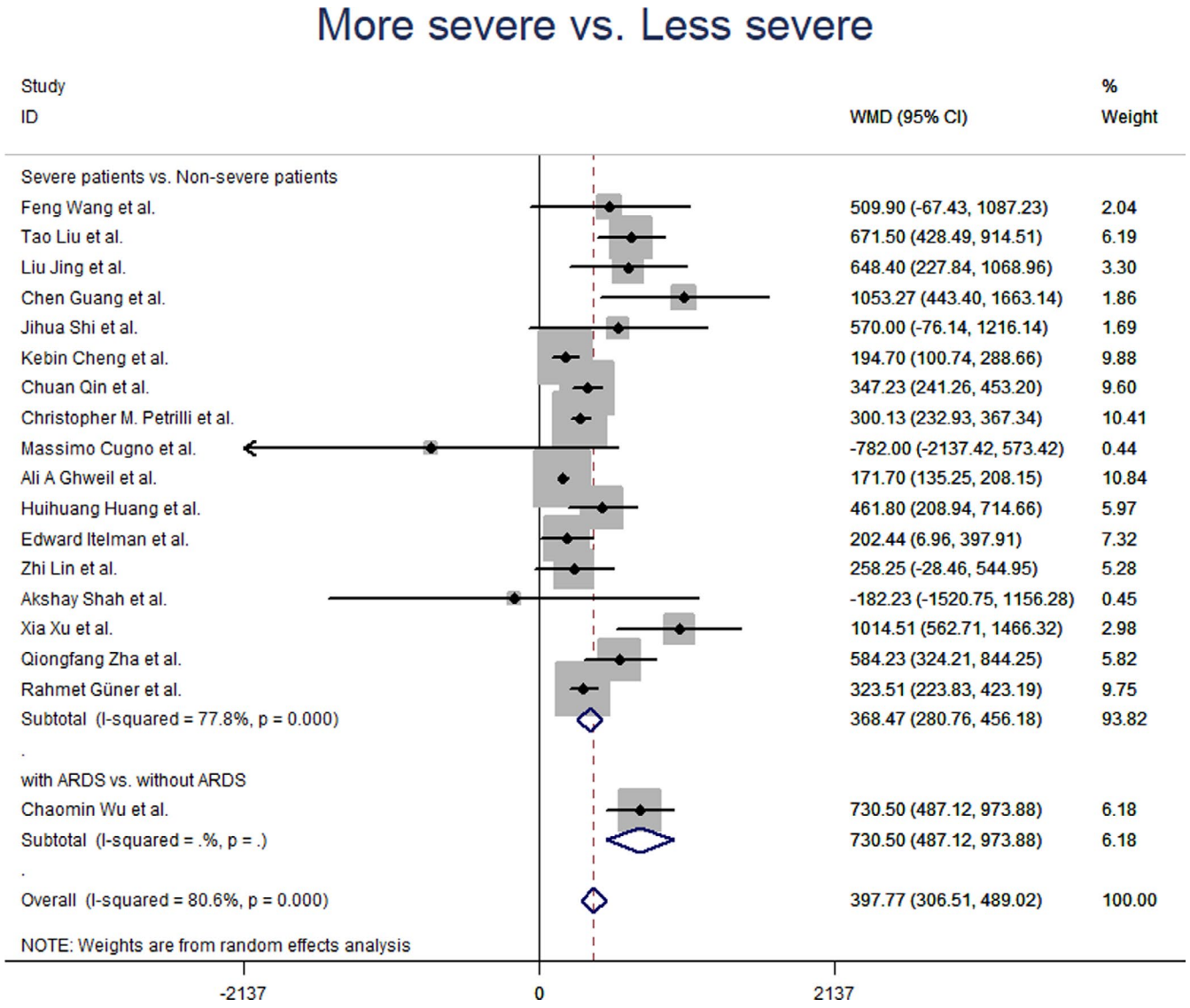

FIGURE 2 Forest plot of the ferritin level between more severe and less severe COVID-19 patients. ARDS: acute respiratory distress syndrome

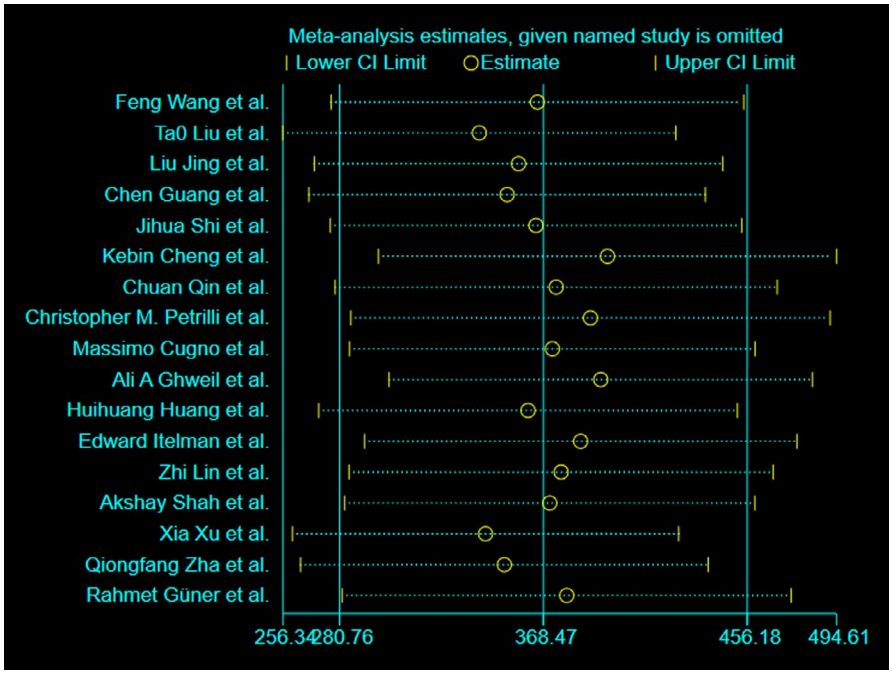

FIGURE 3 Sensitivity analysis of ferritin levels between severe and non-severe COVID-19 patients

bleeding complications, and cerebral ischemia in this meta-analysis, but most of the above subgroups were only included in one study. On the contrary, COVID-19 patients with hypertension had slightly lower levels of ferritin than those patients that were without (WMD −188.19 (95% CI −333.46-42.91)), which is the study of Huang et al[60] (Figure 6). Publication bias was not evaluated due to the small number of included studies.

The ferritin level in male COVID-19 patients versus the female ones was also significantly different [WMD 611.25 (95% CI 434.6-787.91)]; however, only one study by Qin et al[30] was included (Figure 6).

3.5 | Association of ferritin with liver damage

In the single-center study by Da et al in the United States, abnormalities in aminotransferase, lactate dehydrogenase (LDH), and ferritin levels were observed in five cases with COVID-19-related liver injury.[73] Sun et al found that serum ferritin was high in severe and critically ill groups ($P < .001$), and was positively associated with alanine aminotransferase (ALT) ($r = .385$, $P = .002$), aspartate transaminase (AST) ($r = .437$, $P < .001$), and LDH ($r = .394$, $P = .001$) levels, but not with alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT).[74] Multivariable analysis in the study by Phipps et al also revealed that severe acute liver injury was significantly associated with high levels of ferritin (OR 2.40, $P < .001$) and these subsets of patients had a more severe clinical course.[75] Nevertheless, higher levels of ferritin were observed in COVID-19 patients with increased aminotransferases according to Ramachandran et al study, although no statistical difference was observed ($P = .11$).[76]

3.6 | Association of ferritin with treatment

The ferritin level was found related to intensive supportive care in patients with diabetes, including ICU transfer (Figure 7A) and treatment with mechanical ventilation, as demonstrated by Herold et al[33] (Figure 7B), which was in accordance with the study of Cecconi et al[70] Ayanian et al also indicated that high levels of ferritin (≥450 ng/mL) were associated with ICU admission (OR 6.8 (95% CI: 3.4-13.7), intubation (OR 4.0 (95% CI :1.8-8.8), and death (5.1 (95% CI :2.6-10.0).[77] However, our meta-analysis result showed no significant difference in the ferritin levels between ICU versus non-ICU subgroup (WMD 683.95 (95% CI −146.25-1514.15) although they were significant between ICU versus non-ICU when the patients suffered of diabetes (Figure 7A).

In the study of Dimopoulos et al,[78] eight severe COVID-19 patients were positive for the hemophagocytosis score (HScore is composed of nine variables including ferritin[79]) and were diagnosed with secondary hemophagocytic lymphohistiocytosis (sHLH), which can lead to 67% mortality after 28 days. All patients who show a clinical worsening including the increased levels of serum ferritin (maximum concentration 12 670 ng/mL), received anakinra treatment, and improved at the end of the treatment, showing a lower HScore and decreased sHLH parameters including ferritin. In the study by Cavalli et al, COVID-19 patients with ARDS and high inflammatory response (high CRP and ferritin) improved after treatment with a high-dose anakinra, but the study did not mention ferritin as the outcome. However, patients who died or were subjected to mechanical ventilation showed higher baseline levels of ferritin compared with those who survived or were mechanical ventilation-free.[80]

In the study in which off-label tocilizumab was used in 63 patients with severe COVID-19, a significant improvement in laboratory

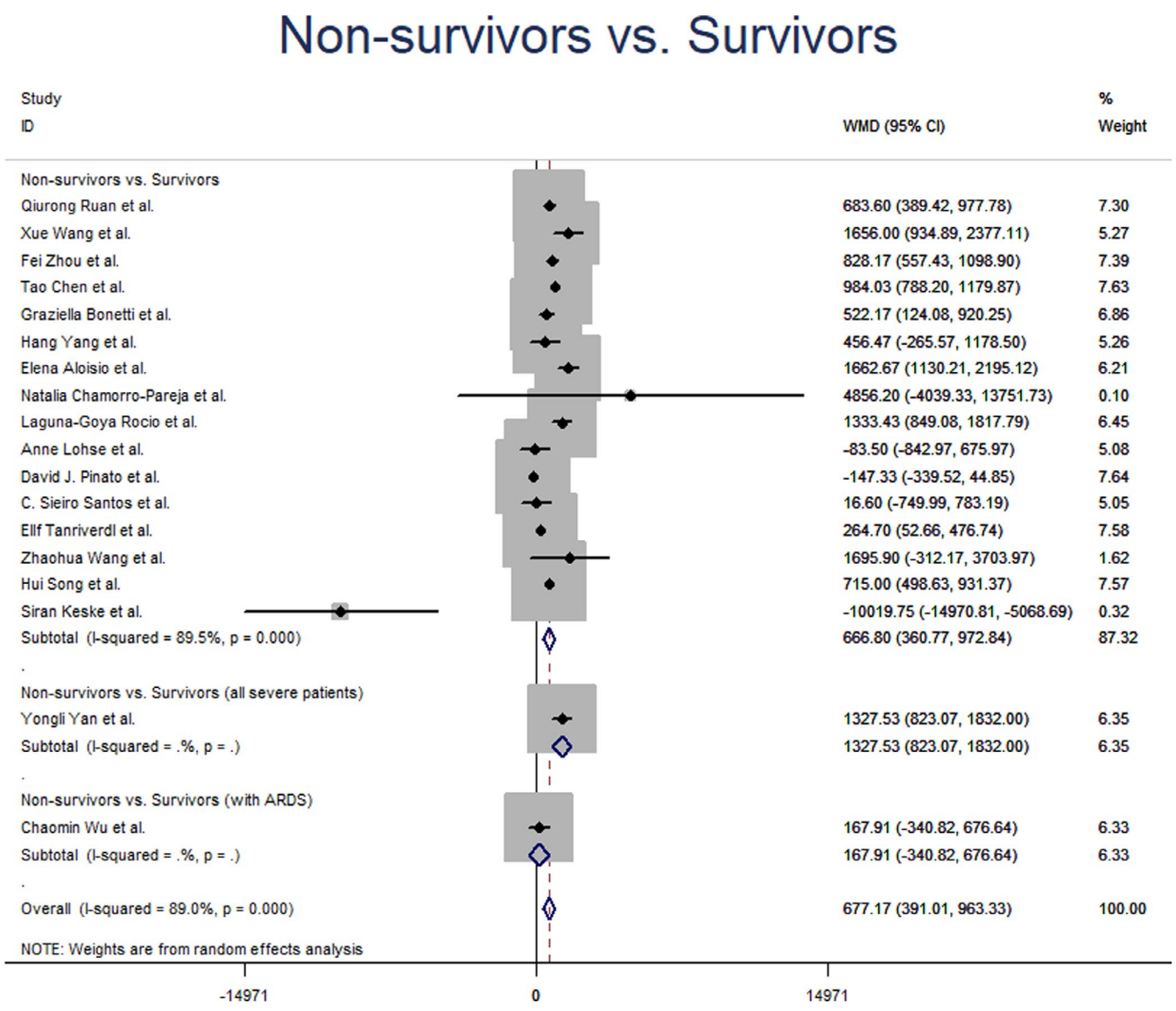

FIGURE 4 Forest plot of the ferritin level between non-survivors and survivors among COVID-19 patients. ARDS, acute respiratory distress syndrome

parameters was observed after treatment, including ferritin, CRP, and D-dimer.[81] Similarly, Toniati et al also showed that tocilizumab can improve the prognosis of COVID-19 patients with ARDS, ferritin, CRP, and fibrinogen levels that steadily decrease after 10 days of tocilizumab treatment.[82] Ramiro et al observed that patients with COVID-19-associated cytokine storm syndrome treated by tocilizumab and glucocorticoids have better treatment benefit, especially those with serum ferritin levels above the median value of 1419 μg/L.[83] However, Pérez-Sáez et al found that the level of CRP rather than the one of ferritin decreases after tocilizumab treatment in patients who need kidney transplant, and the decrease is positively related to survival.[84]

In the study by Sengupta et al, a significant mean reduction of 43% in ferritin level was observed in COVID-19 patients after treatment with exosomes derived from allogeneic bone marrow mesenchymal stem cells.[85]

4 | DISCUSSION

SARS-CoV-2 caused a rapid epidemic worldwide within less than three months. Although most of the patients with COVID-19 have only mild symptoms of infection in the upper respiratory tract without pneumonia, a large proportion of patients develop a severe condition or even face death. It is essential to promptly find out which ones are these severe patients with a potential life-threatening outcome, to perform a targeted intervention and reduce the mortality. In this meta-analysis, a total of 52 studies investigating the association of the ferritin level with the poor outcome of COVID-19 patients or with other clinical characteristics were included. The meta-analysis revealed a role of ferritin in indicating a severe disease in 4992 COVID-19 patients from 18 studies and a mortality risk in 2621 patients from 18 studies. Additionally, COVID-19 patients who were at higher risk because of the comorbidities including

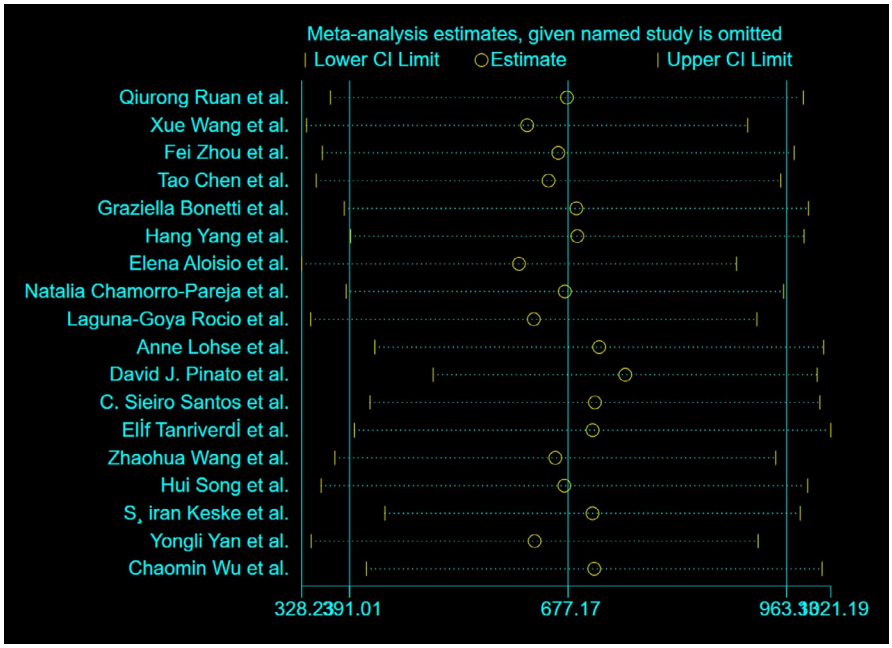

FIGURE 5 Sensitivity analysis of ferritin levels between non-survivors and survivors among COVID-19 patients

diabetes, thrombotic complication, and cancer also showed a higher level of ferritin than that in COVID-19 patients without the same comorbidities.

Ferritin is an iron-storing protein; its serum level reflects the normal iron level and helps the diagnosis of iron deficiency anemia. Circulation ferritin level increases during viral infections and can be a marker of viral replication.[86,87] Increased levels of ferritin due to cytokine storm and sHLH have also been reported in severe COVID-19 patients.[88,89] During the cytokine storm in COVID-19, many inflammatory cytokines are rapidly produced, including IL-6, TNF-α, IL-1β, IL-12, and IFN-γ, which stimulate hepatocytes, Kupffer cells, and macrophages to secrete ferritin.[90] The uncontrolled and dysfunctional immune response associated with macrophage activation, hyperferritinemic syndrome, and thrombotic storm finally leads to multiple organ damage. Notably, ferritin is not only the result of excessive inflammation, but also plays a pathogenic role in the inflammation process through its bind with the T-cell immunoglobulin and mucin domain 2 (TIM-2) by promoting the expression of multiple pro-inflammatory mediators.[7] Besides, some studies showed that H chain of the ferritin activates macrophages to secrete inflammatory cytokines.

Zhou et al revealed that the increase in ferritin level is associated with the worsening of the COVID-19.[6] The cytokine storm and the exaggerated host immune response (ie, ferritin) participate in the development of ARDS, which is the leading cause of mortality if progresses to respiratory failure.[17] In this meta-analysis, higher ferritin levels were found in groups of patients with severe condition or ARDS compared with the levels in less severe patients. However, Wu et al demonstrated that several factors related to ARDS are not associated with the death from ARDS, including ferritin,[17] and this result could be also found from our forest plot of non-survivors versus survivors. The concentration of serum ferritin increases in patients with high mortality risk, which was also observed in this meta-analysis, and its decrease indicates the control of inflammation, thus promoting survival.[7,78]

Hyperferritinemia, regardless of the presence of a tumor or rheumatic disease, is associated with the admission to the intensive care unit and high mortality. To be precise, the concentration of ferritin of more than 500 ng/mL predicts up to 58% mortality.[8,9] As the immune status worsens, ferritin levels increase significantly in patients with sHLH compared with its level in patients with an immune dysregulated status.[89] However, increasing evidence supports the use of anakinra (a recombinant-soluble receptor antagonist of IL-1β and IL-1α) as a first-line treatment in patients with hyperinflammation or sHLH, both characterized by increasing levels of ferritin, which decrease after treatment in the improved patients.[78,80,91] Therefore, serial measurements of ferritin not only help the monitoring of the hyperinflammation status, but also indicate the treatment response. Both patients with decreased ferritin levels less than 50% after treatment show higher mortality.[91,92]

Moreover, our meta-analysis demonstrated that COVID-19 patients who have one or more comorbidities had a significantly higher level of ferritin compared to the ones without comorbidity, suggesting a poor prognosis in patients with comorbidities. Wang et al firstly reported that COVID-19 patients with diabetes have more severe inflammation and higher mortality,[72] while other studies observed that patients with diabetes had higher ferritin levels than those without.[25,29,31,67] The meta-analysis confirmed this results. Meng et al firstly investigated the ferritin levels in COVID-19 patients with cancer, who showed significantly higher levels of ferritin compared with those without.[62] Additionally, other inflammatory markers such as CRP, erythrocyte sedimentation rate, IL-6, and procalcitonin were also present in higher level in COVID-19 patients with cancer, indicating a hyperinflammatory reactions in COVID-19 patients with cancer. The spike protein of SARS-CoV-2 binds the angiotensin-converting enzyme 2 receptor on endothelial cells,[93,94] resulting in

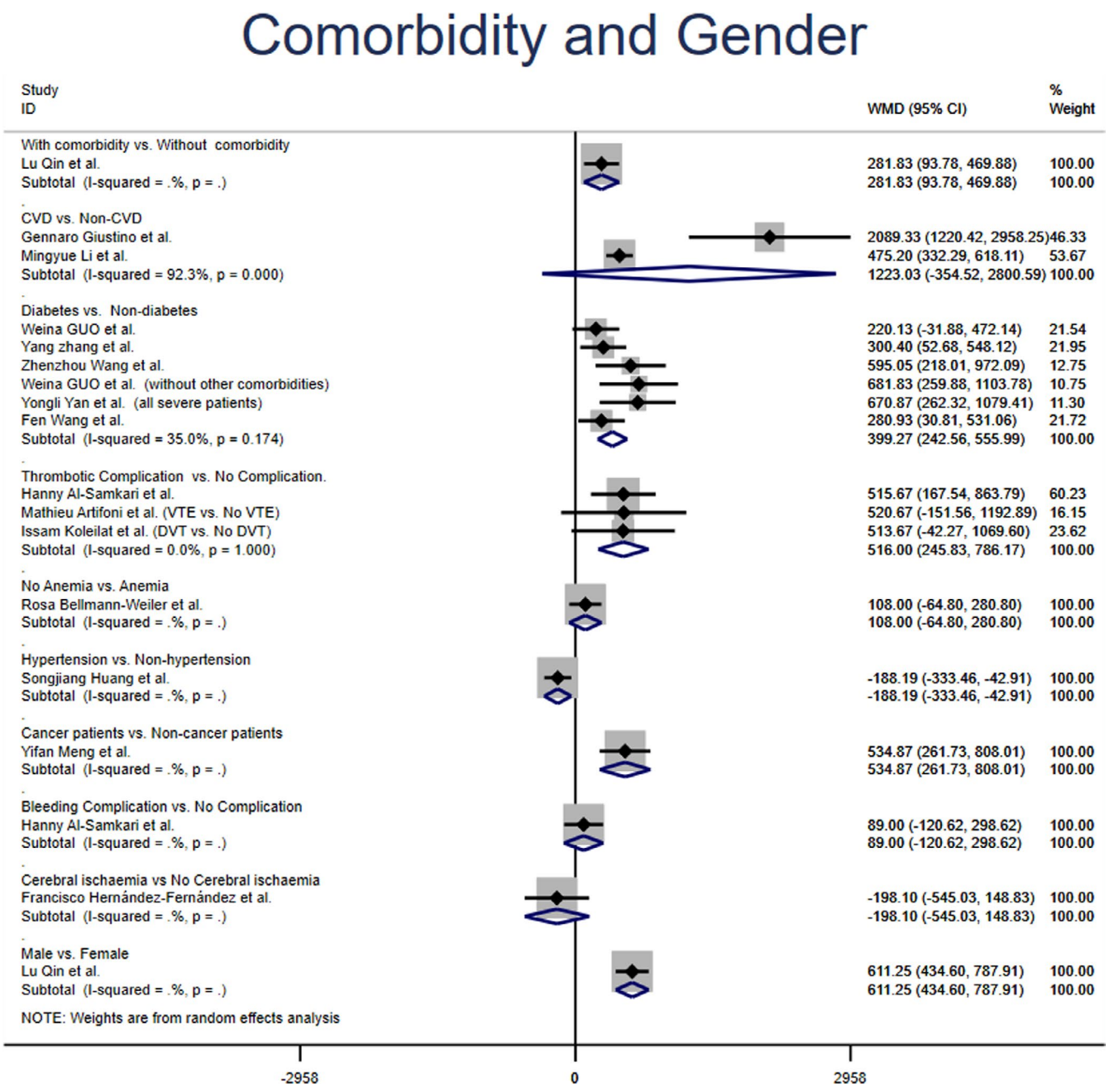

FIGURE 6 Forest plot of the ferritin levels between groups with different baseline information: comorbidity and gender. CVD, cardiovascular disease; DVT, deep venous thrombosis; VTE, venous thromboembolism

endothelial cell apoptosis and thrombosis.[95] Additionally, endothelial cell apoptosis causes inflammatory cell infiltration and further increases in the risk of thrombosis.[96] Accordingly, the meta-analysis indicated that the ferritin levels in COVID-19 patients with thrombotic complications were higher than those in patients without, suggesting the hyperinflammation state in patients with thrombosis. Several studies indicated that high serum ferritin levels are associated with hypertension.[97-99] However, the forest plot by only one study shows that COVID-19 patients with hypertension had lower levels of ferritin compared with those in patients without hypertension; thus, this evidence should be confirmed in further studies.

Notably, the concentration of serum ferritin rarely reaches the HScore threshold (2000 ng/mL) within 16 days after the symptom onset,[6] which limit the early intervention to some extent, but the trend rather than the threshold of the laboratory results provides the most information.[100] Additionally, Li et al found that the ferritin level was the last laboratory value to return to normal compared with other acute proteins, and C-reactive protein returned to normal at least 5 days before ferritin did.[86] Similarly, other studies reported that only C-reactive protein rather than ferritin decreased significantly over time or after treatment.[101,102] Therefore, the decrease at a lower rate limits the use for disease assessment.

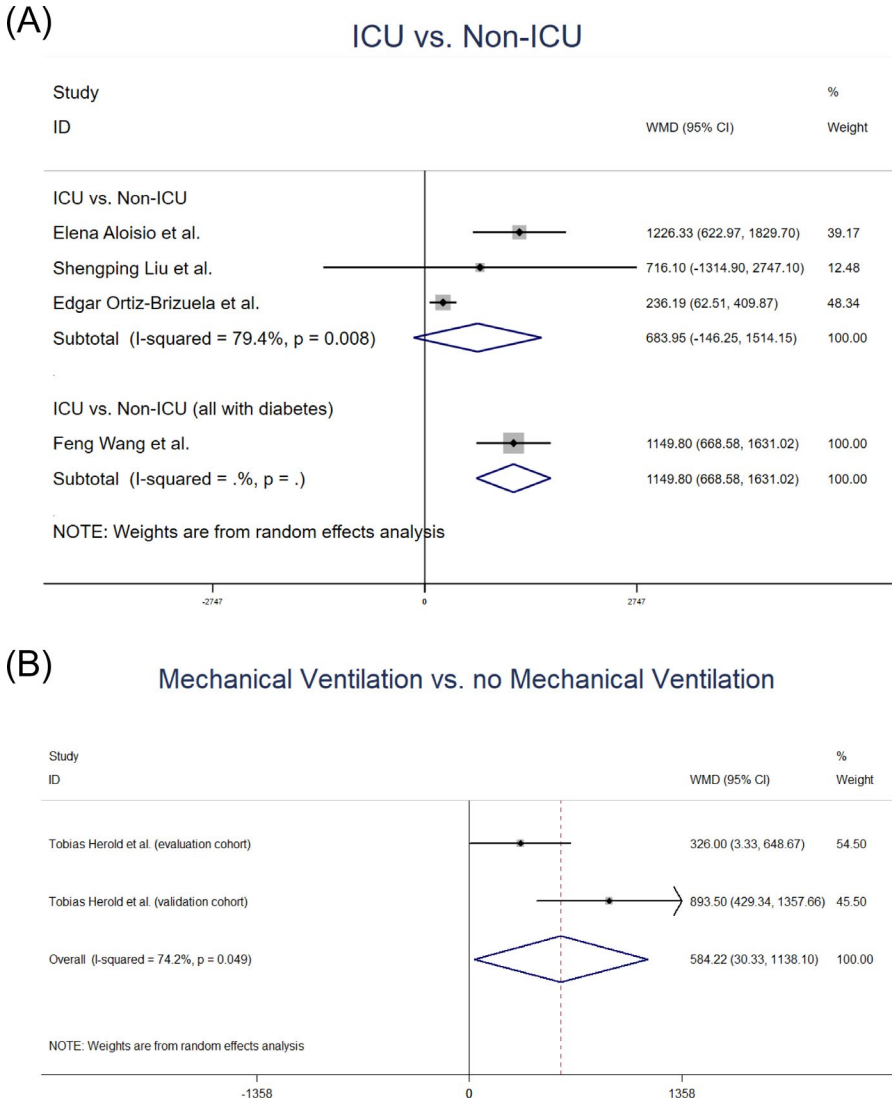

FIGURE 7 Forest plot of the ferritin levels between groups with or without intensive supportive care among COVID-19 patients. A, Forest plot of the ferritin levels between ICU patients and non-ICU patients. B, Forest plot of the ferritin levels between mechanical ventilation and without mechanical ventilation among COVID-19 patients. ICU, intensive care unit

This meta-analysis has some limitations. First, the heterogeneity among studies was significant ($P < .05$). However, the sensitivity analysis revealed the stability of the results and the meta-regression showed no significant effect of age, gender, and case number of the investigation on the pooled results. Other factors including ethnic difference, viral pathogenicity, measurement time or method of ferritin evaluation, and difference in diagnostic and classification criteria due to the constant updates could contribute to such residual heterogeneity. Second, a publication bias was observed in studies with the comparison of severe versus non-severe patients. At present, a large number of articles on COVID-19 have been published, but a delayed publication bias is possible due to the hospitalization of mainly relatively severe COVID-19 patients or the epidemic time point, location bias (most articles from China in this analysis), and potential selective outcome or analysis reporting. Heterogeneity could also contribute to the publication bias.[16] Limited by the number of the included studies, it was not possible to investigate the publication bias of studies in other meta-analysis.[16] Third, although relatively sufficient studies were included regarding the association of ferritin with severity and death, few studies were included in other meta-analysis regarding the clinical relevance of ferritin after databases were extensively searched, suggesting a cautious in the interpretation of the results.

5 | CONCLUSION

This meta-analysis revealed the association between the serum ferritin level and clinical characteristics of COVID-19 patients including disease severity, mortality, comorbidities, and certain treatments. However, the ferritin test is frequently unavailable in an emergency. We recommended that the ferritin test should be screened in patients with COVID-19 to evaluate the presence of hyperinflammation and to predict the worsening and mortality in hospitalized COVID-19 patients. Future clinical studies should be performed to further clarify its prognostic and pathogenic role in COVID-19, and the potential therapeutic value in the inflammation control before end-organ damage.

CONFLICT OF INTERESTS

None.

AUTHOR CONTRIBUTIONS

Linlin Cheng, Haolong Li, and Yongzhe Li conceived and designed the study. Linlin Cheng, Haolong Li, Songxin Yan, and Haizhen Chen acquired the data. Linlin Cheng, Haolong Li, Liubing Li, Chenxi Liu, and Yongzhe Li involved in statistical analysis and interpreted the data. Linlin Cheng and Haolong Li drafted the study. Yongzhe Li, Linlin Cheng, and Haolong Li revised the study. Yongzhe Li supervised the study. All authors read and approved the final study.

ETHICAL APPROVAL

This article does not contain any studies with human participants performed by any of the authors.

DATA AVAILABILITY STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary information.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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