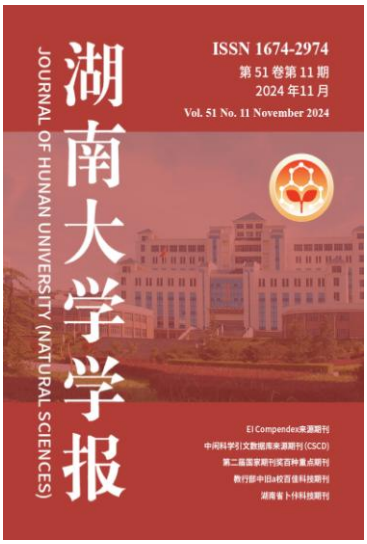

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Predictive Biomarkers in Hypertensive COVID-19 Patients: Systematic Review of Ferritin and D-Dimer Levels

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Abstract: Inflammation and hypercoagulability have been identified as key factors in severe COVID-19, particularly in hospitalized patients with hypertension. Elevated ferritin and D-dimer levels are often associated with worse outcomes, but their effectiveness has not been extensively studied. This study aimed to systematically evaluate the prognostic utility of ferritin and D-dimer in hypertensive COVID-19 patients to determine their individual and combined roles in predicting disease severity and clinical outcomes. The scientific novelty of this work lies in its direct comparison of ferritin and D-dimer, two widely implicated but rarely juxtaposed biomarkers, in the context of hypertensive COVID-19 patients. This review provides a comprehensive analysis of their prognostic value, offering insights into the interplay between hyperinflammation and hypercoagulability in the COVID-19 pathophysiology. This novel perspective could pave the way for biomarker-driven therapeutic interventions for this vulnerable patient population. Scopus, ScienceDirect, Web of Science, and PubMed databases were searched to identify studies published between 2019 and 2023. This systematic review included 25 original

research articles from an initial pool of 1748 records. All selected studies reported the association between ferritin and D-dimer levels and morbidity and mortality in hospitalized hypertensive patients with severe COVID-19. The majority of the included studies showed that elevated ferritin levels were strongly associated with an increased risk of serious outcomes, including ICU admission and mortality. In comparison, although D-dimer levels were also significant predictors, ferritin levels proved to be a more consistent marker. In addition, the prognostic value of these biomarkers was higher in older patients and those with additional comorbidities, suggesting a critical role in risk stratification. Our systematic analysis concluded that elevated ferritin levels are a robust predictor of morbidity and mortality in hospitalized hypertensive patients with severe COVID-19, often outperforming D-dimer levels. This increased risk is influenced by patient age and comorbidities, highlighting the need for further research to optimize clinical management strategies.

Keywords: COVID-19; hypertension; ferritin; D-dimer; morbimortality; risk stratification

高血压新冠肺炎患者的预测性生物标志物：铁蛋白和D-二聚体水平的系统评价

摘要：炎症和高凝状态已被确定为重症新冠肺炎的关键因素，尤其是住院高血压患者。铁蛋白和 D-二聚体水平升高通常与更糟糕的结果相关，但它们的有效性尚未得到广泛研究。本研究旨在系统地评估铁蛋白和 D-二聚体对高血压新冠肺炎患者的预后效用，以确定它们在预测疾病严重程度和临床结果方面的单独和综合作用。这项工作的科学新颖性在于它在高血压 COVID-19 患者的背景下直接比较了铁蛋白和 D-二聚体，这两种生物标志物被广泛提及但很少并列。本综述对它们的预后价值进行了全面分析，深入了解了新冠肺炎病理生理学中炎症过度和高凝状态之间的相互作用。这种新颖的观点可以为针对这一脆弱患者群体的生物标志物驱动的治疗干预铺平道路。我们搜索了 Scopus、ScienceDirect、Web of Science 和 PubMed 数据库，以查找 2019 年至 2023 年期间发表的研究。本系统综述包括来自 1748 条记录的初始池中的 25 篇原创研究文章。所有选定的研究都报告了铁蛋白和 D-二聚体水平与重症新冠肺炎住院高血压患者发病率和死亡率之间的关联。大多数纳入的研究表明，铁蛋白水平升高与严重后果风险增加密切相关，包括 ICU 入院和死亡。相比之下，虽然 D-二聚体水平也是重要的预测指标，但铁蛋白水平被证明是一种更一致的标志物。此外，这些生物标志物的预后价值在老年患者和患有其他合并症的患者中更高，表明在风险分层中起着关键作用。我们的系统分析得出结论，升高的铁蛋白水平是重症新冠肺炎住院高血压患者发病率和死亡率的有力预测指标，通常优于 D-二聚体水平。这种增加的风险受到患者年龄和合并症的影响，凸显了需要进一步研究以优化临床管理策略。

关键词：新冠肺炎; 高血压; 铁蛋白; D-二聚体; 发病率; 死亡率; 风险分层

1. Introduction

COVID-19 was declared a global pandemic in March 2020 by the World Health Organization and is caused by SARS-CoV-2, a member of the Betacoronavirus genus [1], [2]. The clinical presentation of COVID-19 has shown great variability worldwide, making it a social, medical, and scientific challenge owing to its unpredictable and rapid clinical course, which can lead to severe and even fatal complications [3].

Elderly and male patients with comorbidities such as hypertension, diabetes mellitus, and heart disease are at an increased risk of developing severe COVID-19 [4]. Numerous studies have evaluated the evidence related to the pandemic in these patient groups, highlighting the risk factors associated with serious complications and an increased risk of death [5]. Hypertension was identified as the comorbidity most associated with disease severity in patients hospitalized with severe COVID-19 and in those who died. It has been proposed that antihypertensive drugs may increase angiotensin-converting enzyme 2 expression at the cell membrane, facilitating SARS-CoV-2 entry and altering cell function through cytotoxic mechanisms

[6].

A rapid inflammatory response has been observed in patients with severe COVID-19. The results of inflammatory biomarkers in the serum of these patients are key data, as they play a crucial pathophysiological role in COVID-19, correlate with worse prognosis, and serve as key predictors of severity, progression, and in-hospital mortality [7]. Among these biomarkers, high D-dimer and ferritin levels are of particular importance. D-dimer, which is involved in the formation and breakdown of fibrin, is associated with thrombosis when found at high levels [8]. Ferritin is an iron-binding protein that is elevated in infectious diseases and associated with cell damage [9]. Both biomarkers are associated with abnormalities of the vascular wall, pathogenesis and severity of various inflammatory diseases, and regulation of hypertension.

This systematic review rigorously evaluated ferritin and D-dimer levels as predictive biomarkers in hospitalized patients with hypertension and severe COVID-19. Recent studies have demonstrated the superior reliability of ferritin for predicting adverse outcomes, including ICU admission and mortality. This review highlights the increased prognostic value of these biomarkers in older patients and in those with comorbidities, emphasizing their critical role in risk stratification and clinical management. These findings aimed to optimize patient outcomes and reduce mortality through an evidence-based approach for the management of severe COVID-19.

2. Methods and Materials

2.1. Search Strategy

This systematic review was conducted according to PRISMA guidelines [10] and registered in PROSPERO under the code CRD42023440378 [11]. We aimed to include all observational studies (case series, descriptive, cross-sectional, case-control, and cohort) published until December 19, 2023, focusing on the adult population diagnosed with hypertension and hospitalized for severe COVID-19. These studies had to evaluate inflammatory biomarkers, specifically ferritin and D-dimer, to assess their association with morbidity and mortality.

A comprehensive search was conducted using four major databases: Scopus, ScienceDirect, Web of Science, and PubMed. The search covered the period from 2019 to 2023 and used the following Boolean equation: (“Inflammatory biomarkers” [MeSH Terms] OR “Predictors of Morbimortality” [Text Word] OR “Ferritin” [MeSH Terms] OR “D-Dymer” [MeSH Terms]) AND (“Hypertension”) AND (“Severe Covid-19” [MeSH Terms]) AND (“Adult people” [Text Word] OR “Patients hospitalized” [Text Word]).

2.2 Eligibility Criteria

From an initial pool of 1748 records, a careful selection process using the Rayyan AI platform was undertaken to identify studies that met the strict inclusion criteria for this systematic review. This process includes several key steps to ensure the relevance, quality, and applicability of the selected studies.

2.2.1. Initial Screening Using Rayyan AI

The titles and abstracts of all 1748 records were imported into Rayyan AI for the initial screening. Rayyan AI facilitated the efficient and systematic identification of relevant studies by enabling rapid tagging and categorization. Studies that did not focus on the adult population diagnosed with hypertension and hospitalized for severe COVID-19 were excluded. The initial screening significantly reduced the number of potentially eligible articles.

2.2.2. Full Text Review

The full text of the remaining articles was thoroughly reviewed by Rayyan AI. At this stage, the studies were assessed for adherence to the inclusion criteria. Specifically, studies had to be observational (case series, descriptive, cross-sectional, case-control, cohort) and report ferritin and D-dimer levels as well as morbidity and mortality outcomes. Articles that did not meet these criteria were excluded to ensure that only those studies providing relevant and comprehensive data were included.

2.2.3. Quality Assessment

The full text of the remaining articles was thoroughly reviewed by Rayyan AI. At this stage, the studies were assessed for adherence to the inclusion criteria. Specifically, studies had to be observational (case series, descriptive, cross-sectional, case-control, cohort) and report ferritin and D-dimer levels as well as morbidity and mortality outcomes. Articles that did not meet these criteria were excluded to ensure that only those studies providing relevant and comprehensive data were included.

2.2.4. Data Extraction and Synthesis

Detailed data extraction was performed in the remaining studies to capture all relevant information on the prognostic value of ferritin and D-dimer levels. The extracted data were then synthesized to provide a comprehensive overview of how these biomarkers predict morbidity and mortality in a specific patient population. Rayyan AI collaborative features facilitate efficient extraction and synthesis by allowing multiple reviewers to work simultaneously and reconcile differences in real time.

This meticulous and multistage selection process,

facilitated by Rayyan AI, identified 25 original research articles that met the inclusion criteria for this review. Together, these articles provide a robust and reliable dataset for evaluating the comparative predictive values of ferritin and D-dimer levels in hospitalized hypertensive patients with severe COVID-19.

2.3. Inclusion Criteria

To ensure the robustness and relevance of our systematic review, we set strict inclusion criteria for studies to be considered. These criteria are designed to focus on high-quality, relevant research that directly addresses our research question regarding the predictive value of ferritin and D-dimer levels in hospitalized hypertensive patients with severe COVID-19. The inclusion criteria were as follows.

2.3.1. Study Design

Observational studies: Only observational studies were included to capture real-world evidence and ensure comprehensive data collection on the natural history and outcomes of the disease. This category includes a variety of study designs, including: i) case series: reports on a number of patients with common characteristics to identify patterns and outcomes; ii) descriptive studies: provide detailed accounts of disease characteristics and patient outcomes without intervention; iii) cross-sectional studies: analysis of data from a population at one point in time to identify prevalence and correlations between biomarkers and outcomes; iv) case-control studies: compare patients with serious outcomes (cases) to those without (controls) to identify predictive biomarkers; v) cohort studies: follow-up groups of patients over time to assess the relationship between ferritin and D-dimer levels and morbidity and mortality outcomes.

2.3.2. Patient Population

Considering these items: i) Adult patients. Studies must include adult patients (aged 18 years and older) to ensure the applicability of the results to the adult population. This criterion excludes pediatric populations whose disease characteristics and biomarker responses may be significantly different; and ii) diagnosis of hypertension. Patients must have a confirmed diagnosis of hypertension, a common comorbidity in severe COVID-19 cases, and be essential for understanding the interaction between hypertension, COVID-19 severity, and biomarker levels; and iii) hospitalized for severe COVID-19. The focus is on patients hospitalized for severe manifestations of COVID-19, ensuring that the study population represents those at the highest risk of complications and adverse outcomes.

2.3.3. Biomarker Reporting

In terms of i) ferritin levels. Studies must report ferritin levels, an inflammatory biomarker associated with disease severity and prognosis in COVID-19. Ferritin plays a critical role in iron metabolism and its elevation is associated with hyperinflammation) D-dimer levels. Studies must also report D-dimer levels, a fibrin degradation product that indicates coagulation activation and thrombotic events, which are critical in the pathophysiology of severe COVID-19.

2.3.4. Outcome Measures

To ensure that the selected studies provide high-quality, relevant data that can be synthesized to draw meaningful conclusions regarding the role of ferritin and D-dimer as predictors of morbidity and mortality in hospitalized hypertensive patients with severe COVID-19. The selected studies must assess and report outcomes related to morbidity and mortality. This includes measures such as ICU admission rates, length of hospital stay, need for mechanical ventilation, and mortality rate. These outcomes are essential for assessing the prognostic value of ferritin and D-dimer levels and their potential utility in clinical risk stratification and management.

2.3.5. Exclusion Criteria

These exclusion criteria helped to filter out studies that did not meet the specific requirements of this systematic review, ensuring that the final selection was relevant, high-quality, and directly applicable to the research question of this study, as follows: i) Irrelevant Study Population. Studies that did not focus on hospitalized patients with hypertension and severe COVID-19. To maintain the focus on the specific patient population relevant to your review, ensuring that the findings are applicable and targeted; and ii) Inadequate Outcome Measures. Studies that did not report ferritin and D-dimer values or did not assess morbidity and mortality outcomes. To ensure that the studies included in the review provided the necessary data for the analysis of ferritin and D-dimer levels as predictors of morbidity and mortality, and iii) Poor Study Design or Quality. Studies with significant methodological flaws, lack of peer review, or insufficient data (e.g., case reports and small sample sizes without robust statistical analysis). To include only high-quality studies that provided reliable and valid results, thereby strengthening the overall conclusions of the systematic review.

2.4. Synthesis of results

Data from the included studies were synthesized using a narrative approach supported by meta-analytic techniques where appropriate. This synthesis aimed to compare the predictive values of ferritin and D-dimer

levels for morbidity and mortality in hospitalized hypertensive patients with severe COVID-19. The analysis also investigated the effects of age and comorbidities on the prognostic utility of these biomarkers. The results were presented in a structured format, highlighting the prevalence and severity of outcomes and the consistency of findings across studies.

3. Results and Discussion

Figure 1 illustrates the PRISMA flowchart, detailing the strategic selection process of the studies identified through our comprehensive literature search. This figure summarizes the rigorous screening and assessment stages that led to the final inclusion of the studies in this systematic review. Initially, 1748 studies were identified in four databases: Scopus, ScienceDirect, Web of Science, and PubMed.

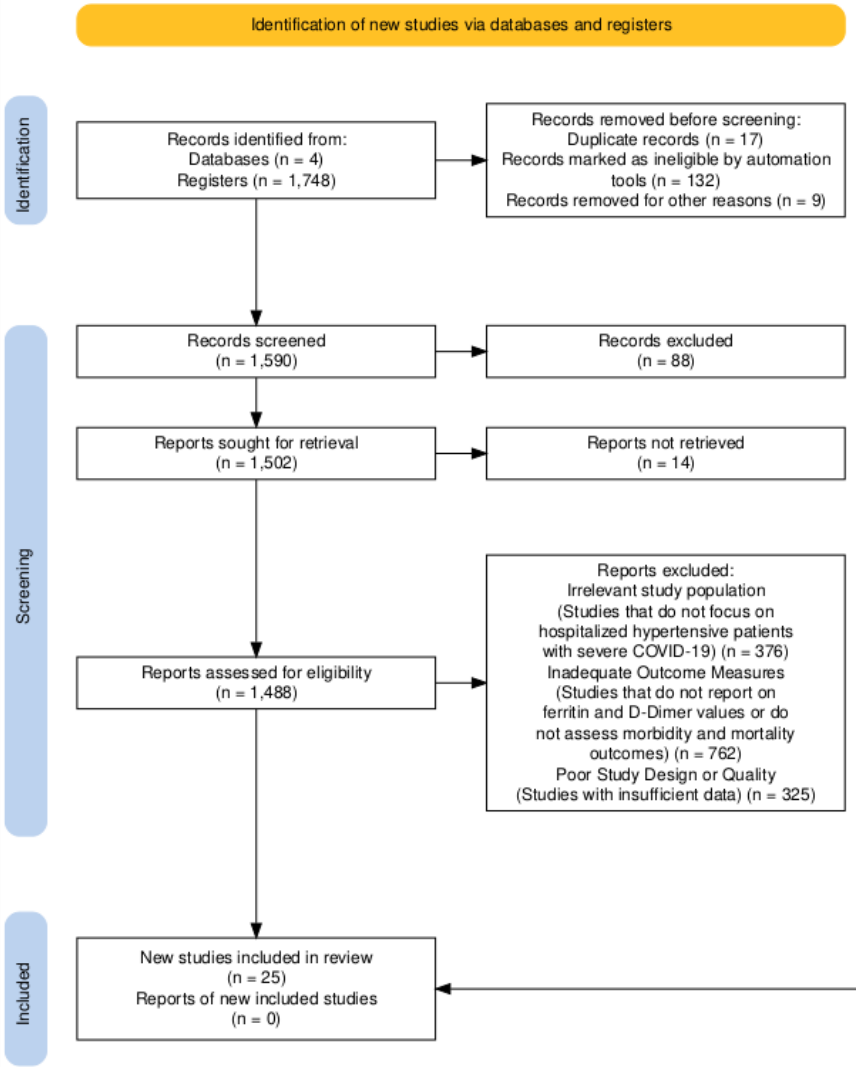

Figure 1. PRISMA flow chart showing in detail the process of identification and selection of studies from databases and registers

Source: Adapted from [10].

3.1. Features of Included Studies

The systematic review included 25 original research articles carefully selected from an initial pool of 1748 records from four major databases and registers. The PRISMA flowchart in Figure 1 details the identification, screening, eligibility, and inclusion processes. The characteristics of the included studies are described below:

3.1.1. Study Design

The selected studies were all observational in nature, provided real-world evidence, and included various designs, such as case series, descriptive studies, cross-sectional studies, case-control studies, and cohort studies. This diversity in study design ensured a comprehensive analysis of the prognostic value of ferritin and D-dimer levels in patients with severe COVID-19.

3.1.2. Patient Population

All studies focused on adult patients diagnosed with hypertension who were hospitalized for severe

COVID-19. This criterion ensured the applicability of the results to a high-risk patient population (Table 1).

Table 1. Analysis of ferritin and D-Dimer values as predictors of morbimortality in hospitalized hypertensive patients with severe COVID-19 (compiled by the authors)

Reference	Ferritin + D-Dimer Comparator Value	Ferritin Value Reported	D-Dimer Value Reported	Patient Population Characteristics	Outcome Measures
Hernández et al. [12]	Ferritin >500 ng/mL and D-dimer >2000 m/mL	Ferritin > 500 ng/mL	D-Dimer >2000 m/ml	502 patients (Male: 314 (62.5%, 95% CI 58-66%); Female: 188 (37.5%, 95% CI 33-42%). Age: Mean: 54.14 ± 13.8 years. Hospital stays: 1-43 days. Mean: 9.8 ± 7.8 days	The primary outcome measures were mortality rate and clinical characteristics associated with mortality, including symptoms, comorbidities, and laboratory markers in COVID-19 patients hospitalized in Puebla, Mexico.
Konya et al. [20]	It does indicate that elevated ferritin and D-dimer levels were independently associated with higher mortality)	Ferritin value above 500 mg/L in 19.7% of patients	1000 µg/l	269 (53.8%) male, 231 (46.2%) female. Age: Mean 57.6 ± 15.1 years, with higher mortality in older patients (mean 72.2 years in those who died vs. 61.3 years in those who survived). Comorbidities: Hypertension (35.2%), diabetes mellitus (22%), COPD (13.4%), cardiovascular diseases (5.8%), renal failure (2.6%)	The primary outcome measured in this study was the mortality rate of COVID-19 patients. The secondary outcomes included the clinical and laboratory characteristics of the patients, such as demographic factors, symptoms, comorbidities, laboratory parameters, radiological findings.
Patil et al. 2022 [14]	_____	Ferritin levels significantly correlate with the duration of illness in COVID-19	Elevated levels of D-dimer were recognised as an indicator of the severity of COVID-19 cases.	Male: 650/1000; Female: 350/1000. Age > 50: 600 cases; < 50: 400 cases. Comorbidities: Diabetes mellitus, ischemic heart disease, hypertension, COPD.	The primary outcome measured in this study was the association between ferritin levels and the development of post-COVID lung fibrosis.
Kara et al. [21]	_____	276 (130-396) µg/L (median with interquartile range)	0.59 (0.33-1.08) µg/mL (median with interquartile range)	312 patients (140 females; 172 males). Mean age was 46.1 ± 14.8 years. Comorbidities: Hypertension (25.0%), obesity (19.2%), diabetes mellitus (11.9%), and bronchial asthma (10.9%).	The severity of COVID-19 disease, categorized into mild, moderate, and severe groups based on clinical and radiological findings. The secondary outcomes were the median length of hospital stay and intensive care treatment.
Radkah et al. [22]	_____	523.40 [455.90–623.69]	763.00 [681.00–952.00]	Male patients were more likely to develop PTE compared to female patients (81.7% vs 41.6%). Other	The incidence of pulmonary thromboembolism (PTE) in COVID-19 patients and the severity

				comorbidities: Not reported	of PTE, as assessed by the simplified Pulmonary Embolism Severity Index (s-PESI) score.
Muhammad et al. [23]	- Ferritin: < 500 ng/ml vs. > 2000 ng/ml - D-dimer: < 3 μg/ml vs. > 3 μg/ml and > 6 μg/ml	Ferritin level > 2000 ng/ml	> 3.0 μg/ml conferred 11-fold and > 6.0 μg/ml conferred 24-fold mortality risk.	Mean age: 58.9 years; Common comorbidities: Hypertension (65.0%), diabetes (50.0%), chronic kidney disease (30.0%), cardiovascular diseases (28.5%)	Primary outcome: In-hospital mortality Secondary outcomes: Need for intensive care unit (ICU) admission; Need for mechanical ventilation; Need for new renal replacement therapy (HD); Need for vasopressors.
Vizcaychipi et al. [24]	_____	The admission ferritin interquartile range is reported as 245-1100 μg/L.	1001-3000 ng/mL, 3001-5000 ng/mL, >5000 ng/mL	Median age: 67 years, with over 25% of patients being at least 81 years old. Gender: 60% male. Comorbidities: Hypertension: 53%; Diabetes: 38%; Asthma: 24%	Mortality rate, number of patients discharged home, number of patients who died.
Para et al. [25]	Ferritin > 3000 ng/mL, D-dimer elevated, and ferritin > 3250 ng/dL	> 3000 ng/mL	_____	Mean age: 68.75 ± 13.22 years. Gender: 65% male, 35% female. Comorbidities: Hypertension (60%); Obesity (23%); Diabetes mellitus (19%).	The primary outcome measured in this study was adverse outcomes, defined as in-hospital mortality or need for intensive care treatment.
Keski [26]		813 ng/mL (deceased) vs 273 ng/mL (surviving)	3660 ng/mL (deceased) vs 713 ng/mL (surviving)	302 hospitalized COVID-19 patients, with a mean age of 57.1 ± 17.6 years and a male to female ratio of 0.961. Comorbidities: Hypertension (38.1%); diabetes mellitus and coronary artery disease.	Mortality rate
Kesmez Can et al. [27]		Asymptomatic: 64.0 (IQR 85.5) Mild/Moderate: 125.5 (IQR 241.0) Severe: 1022.0 (IQR 740.0)	Asymptomatic: 288.0 (IQR 177.5) Mild/Moderate: 548.0 (IQR 471.0) Severe: 2600.0 (IQR 3011.0)	- Mean age: 46.0 ± 19.1 years - Gender: 54.4% male - Most common comorbidity: Hypertension (36.1%)	Clinical classification of COVID-19 cases, frequency of common symptoms, prevalence of comorbidities, proportion of severe cases requiring intensive care, and overall mortality rate. The secondary outcomes were the levels of various laboratory parameters across the different clinical groups.
Casas Rojo et al. [28]		73.5% of patients had high ferritin levels	63.8% of patients had high D-dimer levels	The study population had a median age of 69.4 years, with 57.2% being male. There was a high level of	- Primary outcomes: - Mortality rate: 21.0% - Length of hospital stay: average 10.4 days - Readmission rate:

				comorbidities, with 61.4% having moderate or severe Charlson Comorbidity Index scores and the most common comorbidities being hypertension (50.9%), dyslipidaemia (39.7%), obesity (21.2%), and diabetes mellitus (19.4%).	3.9% within 30 days - Secondary outcomes: - Use of respiratory support: 8.0% high flow nasal cannula, 4.9% non-invasive ventilation, 6.6% invasive mechanical ventilation - Incidence of ARDS: 33.1%
Shakaroun et al. [29]	Ferritin: > 490 ng/mL, CRP: > 10 mg/L, Procalcitonin: > 0.5 ng/mL, D-Dimer: ≥ 1.4 mcg/mL	490 ng/mL - Mean ferritin level on ICU day 1: 649 ng/mL (95% CI 308-1232)	D-Dimer: OR 3.2 (95% CI 2.3-4.4)	2265 patients admitted with COVID-19, of whom 1904 (84%) had a documented ferritin level within 24 hours of admission. The patients had a median age and comorbidities that were similar between those with and without an admission ferritin level.	The primary outcomes measured in this study were mortality rate, ICU admission, and need for mechanical ventilation. The study also assessed whether longitudinal assessment of ferritin levels could predict these outcomes.
Abbattista et al. [30]	High D-dimer (>1.0 ng/mL) and high LDH (>300 U/L), but this does not involve ferritin.	1061 ng/mL (IQR 520-1768)	993 ng/mL (IQR 575-1751)	The study population consisted of 378 patients hospitalized with COVID-19 in Milan, Italy. The majority were male (66%) with a median age of 62 years. Patients who died had a higher median age of 75 years compared to 58 years for survivors	The primary outcome measured in this study was in-hospital mortality rate, which was 22% (83 out of 378 patients). The study also reported the median length of hospital stay for those who died (8 days) and those who survived (19 days).
Altuntas et al. [31]		925.6 ng/mL	1.2 mg/L FEU	61.4 years (average); 32.8% female, 67.2% male; Hypertension: 47.2%; Diabetes mellitus: 32.8%; heart disease: 27.5%; - Average symptom duration: 8.2 days; Average total hospitalization period: 13.1 days; stay for ICU patients: 10.1 days	- Length of hospital stay: 13.1 days on average - Length of ICU stay: 10.1 days on average for those admitted to ICU - Mortality rate: 24% - Proportion still hospitalized at time of data collection: 59.5%
Zayed et al. [32]	Ferritin Comparator Value: > 548.5 ng/mL	954 ± 138 ng/ml	75.8% of patients had positive D-dimer	Group mean age (53.2 ± 12.6 years) Group A (40.3 ± 10.3 years); diabetes mellitus (60.61% vs 16.57%), hypertension (51.52% vs 20.12%), ischemic heart disease (27.27% vs 3.55%), bronchial asthma (36.36% vs 3.55%), COPD (9.09% vs 1.18%), and hyperlipidemia (12.12% vs 2.37%).	- Need for ICU admission - Need for mechanical ventilation - Duration until conversion - Length of hospital stay - Mortality rate
Dong et al. [33]		622.80 μg/L (interquartile	1.80 μg/mL (interquartile	The comorbidity group had a higher proportion of	Primary outcome: Mortality within 28 days

		range 318.45-1,574.00)	range 0.52-9.98)	male patients (94:81) compared to the non-comorbidity group (52:51). Patients in the comorbidity group were older, with a median age of 67 years, compared to 56 years in the non-comorbidity group.	Secondary outcomes: ARDS, ventilation treatment rates, length of hospital stay
Etkin et al. [34]	D-Dimer: 1,000 ng/mL and 5,000 ng/mL	_____	Median: 2,673 ng/mL;	Median age: 67 years; hypertension (53%), diabetes (35%); acute arterial ischemia (45%)	Primary outcomes: Limb loss rate: 18%; In-hospital mortality rate: 46%; Mortality rate for patients with lower limb ischemia: 50%.
El khattab et al. [35]	_____	563 μg/L for non-survivors, compared to a median ferritin level of 116 μg/L for survivors	_____	The study population included 100 patients with mild SARS-CoV-2 infection, with a mean age of 41.51 ± 15.98 years (range 18-81 years), and included 48 males and 52 females. Comorbidities: Hypertension, diabetes mellitus, chronic hepatic diseases.	Mortality rate, need for ICU admission, and need for respiratory support. The secondary outcomes were the association of CRP levels on admission with these outcomes, as well as the association of certain patient characteristics (age, comorbidities) with mortality.
Eleni et al. [36]	_____	195 (106-365) ng/mL	0.365 (0-1.07) μg/mL	60 years, with 45.9% aged 65 or older. 57.7% were male, and 30.6% were smokers or ex-smokers. Hypertension (45.6%), diabetes (20%), solid tumors (17.7%), COPD (9.4%), coronary artery disease (9.4%), immunosuppression (8.5%), and chronic kidney disease (4.7%).	The primary outcomes measured in this study were ICU admission and in-hospital mortality. The length of hospital stay was also reported, but not explicitly stated as a primary or secondary outcome.
Ashtorab et al. [13]	_____	2.32 (1.79–3.02) ng/mL	4.75 (2.82–8.02) μg/mL	5,852 hospitalized COVID-19 patients. Median age: 61 years. Hypertension (57.7% overall); Diabetes mellitus (34.1% overall) Cardiac disease (13.1%); COPD (9.8%); Asthma (9.8%); History of cancer (8.4%); Immunosuppression (5.3%)	The mortality rate from COVID-19, which was 14.5% overall. The study also identified age as a strong predictor of mortality, with those over 75 years old having a 10-fold higher risk of death compared to those under 35.

3.1.3. Biomarkers assessed

Each study reported serum ferritin and D-dimer levels, which are the key biomarkers associated with inflammation and coagulation, respectively (Table 1). These biomarkers were assessed for their potential to predict morbidity and mortality in the studied population.

3.1.4. Outcome Measures

The primary outcomes of interest (Table 1) were morbidity and mortality, specifically ICU admission rate, length of hospital stay, need for mechanical ventilation, and all-cause mortality. Consistent reporting of these outcomes across trials facilitated a robust comparative analysis.

3.2. General Interpretation of the Results

Table 1 shows the role of ferritin and D-dimer levels as predictors of morbidity and mortality in hospitalized patients with hypertension and severe COVID-19. Elevated levels of both biomarkers were consistently associated with worse outcomes including increased mortality and more severe disease manifestations. In particular, high ferritin levels were associated with a

higher risk of adverse outcomes such as admission to intensive care and longer hospital stays. This systematic review consolidates findings from several studies [12]-[36] and highlights that older age, male sex, comorbidities such as hypertension, diabetes, and cardiovascular disease, as well as laboratory abnormalities such as lymphopenia and elevated CRP, D-dimer, and ferritin levels, are significant predictors of higher mortality and more severe disease in COVID-19 patients.

3.3. Ferritin as a Crucial Inflammatory Marker

Ferritin has emerged as a key inflammatory marker of COVID-19 pneumonia. Elevated levels were significantly associated with severe disease, poor outcomes, and development of lung fibrosis after COVID-19. Notably, even patients with normal initial ferritin levels can develop lung fibrosis if their ferritin levels increase significantly during hospitalization [14]. This highlights the importance of continuously monitoring ferritin levels as a dynamic predictor of disease progression and complications after COVID. Studies in this review also correlated high ferritin levels with CT severity, disease duration, oxygen saturation, and the need for BIPAP/NIV, making it a valuable tool for patient management [15]-[16].

These findings are consistent with existing literature identifying ferritin as a key inflammatory biomarker in the context of COVID-19 [16]-[18]. The robust association between elevated ferritin levels and poor clinical outcomes highlights the need for the early identification and continuous monitoring of at-risk patients. The consistency of these findings across multiple studies further supports the potential of ferritin as an essential tool for risk stratification in clinical practice, enabling healthcare providers to prioritize interventions for those most at risk [15], [19].

3.4. Limitations of the Included Evidence

Although the review process was rigorous, it was not without its limitations. The reliance on four major databases, Scopus, ScienceDirect, Web of Science, and PubMed, may have inadvertently excluded relevant studies not indexed in these sources. Although a careful selection process was used, the potential for publication bias remains, as studies with negative or inconclusive results are less likely to be published and, therefore, included in this review. In addition, although the use of Rayyan AI for bias assessment helped ensure the quality of the included studies, the subjective nature of certain quality assessment criteria cannot be completely eliminated.

3.5. Implications for Practice, Policy, and Future Research

The results of this review have important implications for clinical practice and policies. The strong association between elevated ferritin levels and serious outcomes in COVID-19 patients highlights the need for routine screening and monitoring of this biomarker in hospitalized patients, particularly those with hypertension. Clinicians should consider incorporating the assessment of ferritin levels into standard COVID-19 care protocols to facilitate early identification of high-risk patients and allow for tailored interventions.

From a policy perspective, these findings support the allocation of resources to improve the diagnostic infrastructure of inflammatory biomarkers in healthcare settings. Ensuring that hospitals are equipped to measure and monitor ferritin levels can improve patient outcomes and reduce the burden on critical care facilities.

Future research should address the limitations of this review. Large-scale multicenter cohort studies are essential to validate the prognostic value of ferritin and D-dimer levels in different populations. Interventional studies investigating the impact of targeted treatments based on ferritin levels may provide valuable insights into potential therapeutic strategies. Investigating the underlying mechanisms linking ferritin to severe COVID-19 outcomes may also reveal novel targets for intervention, ultimately improving patient care and outcomes in this challenging clinical context.

4. Conclusion

This systematic review conclusively identified elevated ferritin level as a superior and consistent predictor of severe outcomes, including ICU admission and mortality, in hospitalized hypertensive COVID-19 patients. Compared with D-dimer, ferritin showed greater reliability across multiple studies. The prognostic significance of these biomarkers is particularly pronounced in older patients and in those with additional comorbidities, highlighting their critical role in risk stratification. Incorporating ferritin into clinical management protocols could significantly improve patient outcomes and reduce mortality, supporting its use as a key marker for the management of severe COVID-19.

Furthermore, the scientific contribution of this work lies in its novel focus on hypertensive COVID-19 patients, a subgroup often overlooked in biomarker research, despite their increased vulnerability. This study is one of the first to directly compare ferritin and D-dimer levels in this population, synthesizing evidence to highlight the superior prognostic value of ferritin. By addressing a critical gap in the literature, this review not only advances the understanding of the interplay between hyperinflammation and serious outcomes but also provides actionable insights to inform clinical decision-making in high-risk

populations.

In light of these findings, this study strongly recommends the routine inclusion of ferritin assessment in clinical protocols for hypertensive patients with coronavirus disease 2019 (COVID-19), particularly during the initial evaluation and ongoing monitoring of those at high risk for severe outcomes. Such integration could enhance the early identification of critical cases, optimize resource allocation in clinical settings, and inform personalized therapeutic strategies.

From a research perspective, these findings highlight the necessity for further investigations into the mechanistic pathways linking hyperferritinemia to severe disease progression. Future studies should also examine the combined predictive power of ferritin and other biomarkers in broader patient populations and evaluate their potential for guiding targeted interventions. By addressing these gaps, subsequent research could refine biomarker-based approaches to risk stratification and expand their applicability to diverse clinical contexts.

Declarations

Author Contributions

Conceptualization, B.G.O. and D.F.L.M.; methodology, B.G.O., L.F.E.C., D.A.V.A., J.C.C.O., M.A.C.M. and D.F.L.M.; software, B.G.O. and D.F.L.M.; validation, B.G.O., L.F.E.C., D.A.V.A., J.C.C.O., M.A.C.M. and D.F.L.M.; formal analysis, B.G.O. and D.F.L.M.; investigation, B.G.O., D.F.L.M. and C.D.C.M.; resources, B.G.O. and D.F.L.M.; data curation, B.G.O. and D.F.L.M.; writing—original draft preparation, all authors contributed equally; writing—review and editing, B.G.O., L.F.E.C., D.A.V.A., J.C.C.O., M.A.C.M. and D.F.L.M.; visualization, B.G.O. and D.F.L.M.; supervision, B.G.O. and D.F.L.M.; project administration, B.G.O. and D.F.L.M.; funding acquisition, B.G.O. and D.F.L.M. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

The data presented in this study are openly available in PROSPERO at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023440378, reference number CRD42023440378.

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Conflicts of Interest

The authors declare that there is no conflict of interests regarding the publication of this manuscript. In addition, the ethical issues, including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancies have been completely observed by the authors.

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