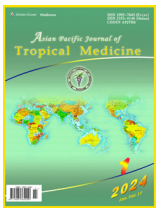

Review Article

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Ferritin and mortality in hemodialysis patients with COVID-19: A systematic review and meta-analysis

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ABSTRACT

Objective: To investigate the difference in serum ferritin levels between deceased and surviving regular hemodialysis patients with COVID-19.

Methods: We conducted a systematic search across four databases following the PRISMA statement guidelines. Studies reporting ferritin levels and mortality of regular hemodialysis patients with COVID-19 were included. Employing the random-effects model, we performed a meta-analysis to determine the mean difference in serum ferritin levels between the studied groups, along with their corresponding 95% confidence intervals. The meta-analysis was carried out using Review Manager 5.4 and Stata 16.

Results: A total of 1 013 patients from seven studies were included in this study. Our meta-analysis showed higher mean serum ferritin in the deceased compared to surviving regular hemodialysis patients with COVID-19, with a mean difference of 449.43 ng/mL [95% *CI* (244.07, 654.80), $P<0.000\,1$; $I^2=58\%$, $P=0.003$].

Conclusions: Our study found a higher mean of serum ferritin levels in the deceased compared to surviving regular hemodialysis patients with COVID-19.

KEYWORDS: Ferritin; Mortality; Hemodialysis; COVID-19; Inflammation

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new beta coronavirus responsible for the global pandemic of coronavirus disease 2019 (COVID-19)[1]. COVID-19 may manifest as severe pneumonia and lead to complications, including acute respiratory distress syndrome (ARDS), respiratory failure, sepsis, septic shock, or multi-organ failure, which may require intensive care and mechanical ventilation[2]. Moreover, the presence of comorbid conditions, such as chronic kidney disease (CKD), would increase the risk of severity and mortality in COVID-19[3].

Patients with CKD have a higher risk of contracting COVID-19,

Significance

In COVID-19, a prognostic marker is needed to stratify patients into high-risk groups in order to ensure adequate and timely care, especially in overwhelmed medical facilities and limited resource settings. Various studies have shown an association between ferritin levels and mortality in COVID-19; however, it remains unclear whether ferritin levels can serve as a prognostic marker in hemodialysis patients, who typically have higher baseline ferritin levels. Therefore, this study aims to investigate the difference in serum ferritin levels between deceased and surviving regular hemodialysis patients with COVID-19.

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with an infection rate of 16% and a prevalence of more than 45%[4]. This risk is even higher for those undergoing renal replacement therapy, such as hemodialysis (HD), who face an increased risk of severe complications and mortality[5,6]. A study by Rastad *et al* found that patients with end-stage renal disease (ESRD) had a 2.5 times higher risk of in-hospital mortality[7].

While the factors responsible for poor outcomes in some COVID-19 patients are not yet fully understood, it is known that the pathogenesis of COVID-19 involves an increased production of proinflammatory cytokines leading to a cytokine storm, particularly in severe cases. This can trigger systemic hyperinflammatory conditions, hypercoagulation, and disturbances in iron homeostasis, which are often associated with an increase in serum ferritin levels[8,9].

Serum ferritin is a marker of iron stores and associated with long-term mortality in regular HD patients[10]. In COVID-19, various studies have shown an association between ferritin and mortality; however, it remains unclear whether ferritin levels can be used as a prognostic marker of mortality in HD patients, who typically have higher baseline ferritin levels than non-HD patients[3,5].

A prognostic marker is needed to stratify patients into a high-risk group and ensure adequate and timely personalized care based on the patient's condition, especially in a limited resource setting. Ferritin is one of the promising markers that is widely available and commonly used in regular HD patients. Therefore, this study aimed to investigate the difference in serum ferritin levels between deceased and surviving regular HD patients with COVID-19.

2. Subjects and methods

2.1. Eligibility criteria

Studies were included in this study if they met the following inclusion criteria: representation for clinical question (P: regular hemodialysis patients with positive/confirmed case of COVID-19; I: a deceased group of patients; C: a surviving group of patients; O: serum ferritin levels). The type of study included in this study were cross-sectional, cohort, and case-control. We excluded non-research articles (*e.g.*: case report or series, review articles, letters to the editor, study protocols, editorials, or commentaries), studies with insufficient data, articles on research in pediatric population (17 years of age or younger), and non-English articles.

2.2. Search strategy and study selection

This meta-analysis was accomplished according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[11]. We systematically searched PubMed, Europe PMC, Cochrane Central Register of Controlled Trials (CENTRAL), and Directory of Open Access Journal (DOAJ) with the following search terms: ("Coronavirus Disease 2019" OR "COVID-19" OR "novel coronavirus pneumonia" OR "2019-nCoV" OR "SARS-CoV-2") AND ("ferritin") AND ("hemodialysis" OR "dialysis") AND ("mortality") on February, 2023. Search results were limited to the last 10 years. Duplicate results were removed initially. The remaining articles were independently screened for relevance by their abstracts with authors. These articles were thoroughly read and those that fulfilled our criteria were included in the study. The final inclusion of studies was merely based on the agreements of all authors. Any disagreement was resolved by consensus. The full text of residual articles was assessed according to the inclusion and exclusion criteria.

2.3. Data extraction

Data extraction was performed independently by authors and using standardized forms that include author, year of study, country of study, study design, number of samples, age, ferritin levels and quality of studies. The variable of interest in our meta-analysis was serum ferritin in mean±SD or median (IQR) from each group of deceased regular hemodialysis patients with COVID-19 and surviving group.

Two review authors independently screened the titles and abstracts of initial search results from the electronic databases after excluding the duplicate and irrelevant studies using Endnote software. After screening for the eligibility, the co-authors retrieved full text of all potentially relevant articles and extracted maximum possible data. A few eligible studies did not report all the relevant information. In such cases, we tried to obtain the information through algebraic back calculation of the available information using the standard formula, or by contacting the authors.

2.4. Quality assessment

The risk of bias of each study were assessed with Risk of Bias in Non-Randomized Studies-of Exposures (ROBINS-E)[12]. The ROBINS-E is a tool that provides a structured approach to assessing the risk of bias in observational epidemiological studies for systematic reviews and meta-analysis. Each bias domain in ROBINS-E is addressed using a series of signaling questions that aim to gather important information about the study and the analysis being assessed.

Two reviewer authors assessed the risk of bias in seven different

methodological aspects (called domains) independently. Per ROBINS-E protocol, risk of bias in each domain was graded as either low, some, high, or very high. In the event of a dispute, it must be addressed by discussion or consultation and came to a consensus with the participation of a third author. Overall risk of bias for each study was then recorded as the highest risk of bias for any domain. Item level judgement for each domain of bias was recorded as the most dominant risk of bias.

2.5. Statistical analysis

We used Review Manager 5.4 (Copenhagen: The Cochrane Collaboration, 2020) and Stata version 16 (StataCorp LP, Texas 77845, USA) to perform the meta-analysis. The effects of the ferritin levels to mortality in HD regular patients complicated with COVID-19 were analyzed by comparing the mean difference between deceased and surviving group. We convert all ferritin levels to ng/mL as the international unit. The mean difference was reported with a 95% Confidence Interval (*CI*). The *P* value was two-tailed, and statistical significance was set at < 0.05.

Heterogeneity was assessed with the Q-statistic test and I^2 test. The I^2 statistic measured the percentage of total variation across the studies due to clinical or methodological heterogeneity instead of chance. If the significant Q statistics ($P<0.1$) indicated heterogeneity across the studies, a random-effect model was utilized. Otherwise, a fixed-effect model was utilized. Substantial heterogeneity was

Table 1. The demographic and clinical characteristics of included studies.

Author	Year	Country	Study design	Sample size (Male/Female)	Age (years)
Fisher *et al.*[19]	2020	USA	Retrospective cohort	114 (70/44)	64.5 (55-73)*
Hakami *et al.*[15]	2021	Saudi Arabia	Retrospective cohort	101 (58/43)	21-45 years: *n*=32 46-64 years: *n*=31 65-98 years: *n*=38
Hendra *et al.*[16]	2021	United Kingdom	Retrospective cohort	148 (84/64)	64.1±14.6†
Islam *et al.*[18]	2020	Turkey	Retrospective cohort	34 (15/19)	62.0±13.2†
Sipahi *et al.*[17]	2021	Turkey	Cross-sectional	23 (14/9)	67(35-91)*
Turgutalp *et al.*[14]	2021	Turkey	Retrospective cohort	567 (296/271)	63(53-71)*
Donati *et al.*[20]	2022	Italy	Case-control	26 (14/12)	70±15†

*Median (interquartile range); †Mean±standard deviation.

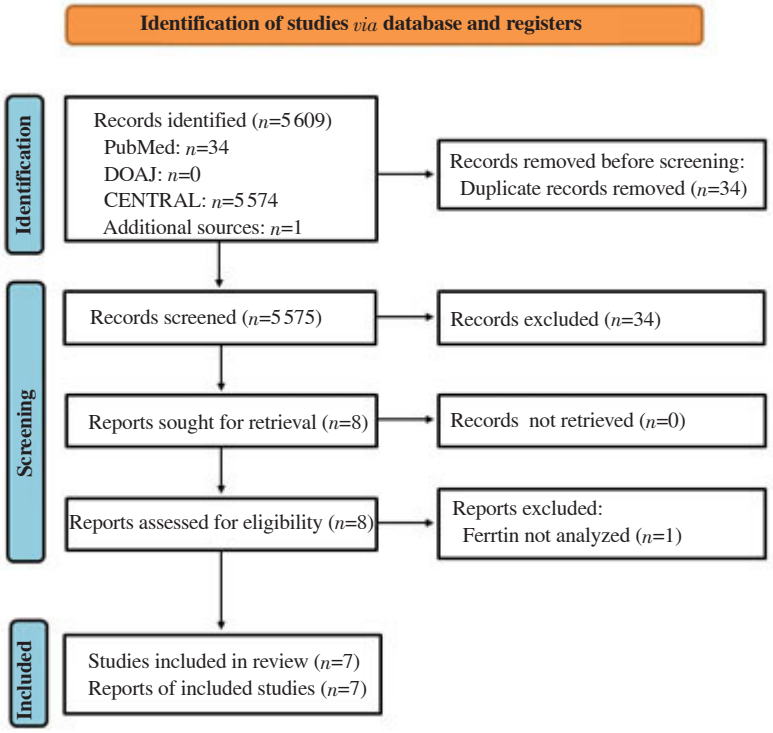

Figure 1. PRISMA flow diagram.

Table 2. Risk of bias with ROBINS-E tool.

Items	Donati *et al.*[20]	Fisher *et al.*[19]	Hakami *et al.*[15]	Hendra *et al.*[16]	Islami *et al.*[18]	Sipahi *et al.*[17]	Turgutalp *et al.*[14]
Risk of bias due to confounding	High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Risk of bias arising from measurement of the exposure	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Risk of bias in selection of participants into the study	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Risk of bias due to post-exposure interventions	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Risk of bias due to missing data	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Risk of bias arising from measurement of the outcome	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Risk of bias in selection of the reported result	High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Overall bias	High risk	High risk	High risk	High risk	High risk	High risk	High risk

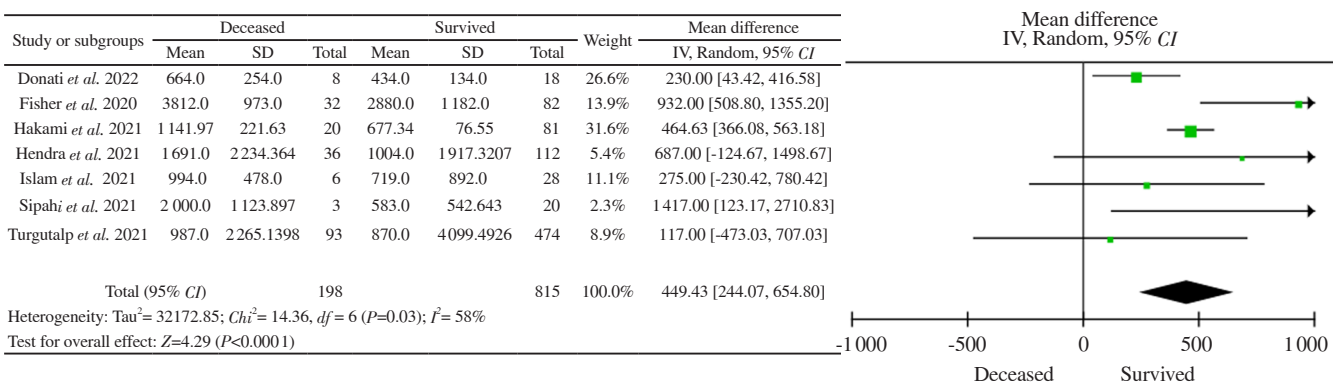

Figure 2. Mean serum ferritin and mortality in regular hemodialysis patients with COVID-19.

represented by I^2 for >50%[13]. We analyzed the difference of mean serum ferritin levels in deceased regular hemodialysis patients with COVID-19 compared to surviving group.

3. Results

3.1. Baseline characteristics and study selection

A total of 1 013 patients from 7 studies were included in qualitative and quantitative synthesis (meta-analysis) (Figure 1)[14–20]. Study characteristics of included studies are presented in Table 1. All the studies were observational studies. Most of the countries were in Europe with one study from Saudi Arabia. Fifty three percent of samples included in this meta-analysis were male.

3.2. Ferritin and mortality

Seven studied were analyzed for their ferritin levels to mortality. The mean difference of ferritin levels between deceased and surviving hemodialysis regular patients with COVID-19 was higher in deceased patients [449.43 ng/mL (95% *CI* 244.07, 654.80), $P<0.000\,1$; I^2=58%, P=0.003] (Figure 2).

3.3. Risk of bias

The risk of bias of each study was assessed using ROBINS-E tool from Cochrane (Table 2). Observational studies assessed had high risk of bias. The funnel plot is shown in Figure 3.

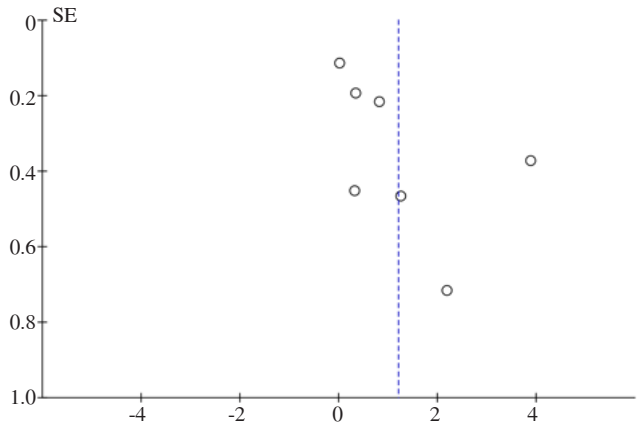

Figure 3. Funnel plots of this study.

4. Discussion

Serum ferritin has been long studied as a marker of iron metabolism and commonly use as guide to iron therapy in CKD patients[21]. Serum ferritin is influenced by inflammatory conditions such as infection, chronic disease, and cancer, therefore, ferritin widely recognized as an acute phase reactant and marker of acute and chronic inflammation[22].

Study by Kalantar Zadeh *et al* showed that high ferritin level is associated with long-term mortality in regular HD patients and further study showed that the association between the serum ferritin and mortality in hemodialysis patient is influenced by the inflammation condition[10,23]. The association between serum ferritin and mortality risk also showed a different pattern in the presence and absence of inflammation[24]. The application as a biomarker of inflammation has gained high importance in the context of COVID-19 progression, as demonstrated by previous studies in the field[25]. Ferritin is found higher in severe COVID-19 patients and as one of markers of cytokine storm[26–28].

The prognostic factor that will help to stratify patients into a high-risk group is essential to ensure adequate and in-time personalized care based on patient's conditions. A study by Cheng *et al* showed that non-survivors had a significantly higher weighted mean difference of ferritin level compared with survivors 677.17 (95% *CI* 391.01, 963.33), $P<0.001$][6]. However, the role of ferritin as a prognostic factor in regular HD patients where the baseline ferritin was higher than the general population or non-dialysis CKD, has not yet been studied[5]. This study showed a statistically significant difference in mean serum ferritin levels between the deceased and surviving regular hemodialysis patients with COVID-19, with a higher level observed in the deceased group.

Ferritin is not only an acute phase reactant, but also a mediator of immune dysregulation during cytokine storms, especially in severe COVID-19[29]. Inflammatory cytokines such as interleukins, tumor necrosis factors, and interferons are rapidly secreted during cytokine storms, which in turn upregulate the production of ferritin by hepatocytes, Kupffer cells, and macrophages[6,30]. Hyperinflammatory conditions in COVID-19 may cause an increase in hepcidin levels which will decrease serum iron due to intracellular iron retention and be stored in the form of ferritin[31,32]. There are three factors associated with an increase of ferritin expression: elevated serum iron, hypoxic conditions, and inflammation[33].

Concurrently, ferritin also induces the release of pro-inflammatory and anti-inflammatory cytokines[6]. The role of ferritin in the cytokine storm explained its role as a predictor for poor outcomes in various conditions[34]. Consistent with this, prospective cohort of 106 outpatient HD patients found that inflammatory markers were risk factors for death and hospitalization[35]. The role of ferritin as a mortality predictor in regular HD patients was supported by the study of Bataille *et al* on regular HD patients that reported an increase in serum ferritin levels until 275% from baseline after COVID-19[36].

Hyperinflammation is a primary pathophysiology in COVID-19 and cytokine profile resembling secondary hemophagocytic lymphohistiocytosis is associated with severe COVID-19[28]. Various lines of evidence have shown that increased ferritin levels in COVID-19 act as markers of inflammation and play a role in the pathophysiology of COVID-19[37]. Hyperferritinemia conditions can lead to iron toxicity and organ damage due to ferroptosis, a non-apoptotic programmed cell death caused by the accumulation of reactive oxygen species (ROS), which triggers lipid peroxidation[13,38]. Iron overload can also result in the accumulation of lipid ROS[39]. This aligns with the findings of the study by Park *et al*, which showed that the association between serum ferritin and mortality risk in hemodialysis patients was independent of systemic inflammation and nutritional status[40].

There are variable results of other inflammatory markers, such as *D*-dimer, procalcitonin, or C-reactive protein (CRP) as an outcome predictor in hemodialysis patients with COVID-19. The study by Beck *et al* during Omicron variant surge, in a high vaccination coverage setting, showed no differences in the level of *D*-dimer, procalcitonin, and CRP between the survivor and non-survivor groups of regular hemodialysis patients with COVID-19[41]. Study by Hendra *et al*, Islam *et al*, and Fisher *et al* showed that CRP, but not *D*-dimer was associated with mortality in hemodialysis patient with COVID-19[16,18,19].

Study on IL-6 by Donati *et al* and Fisher *et al* showed that IL-6 was associated with mortality in hemodialysis patients with COVID-19[19,20]. Meta-analysis by Melo *et al* that also showed role of ferritin in the assessment of the systemic hyper-inflammation and the relationship

between hyperferritinemia and high levels of IL-6 among adult patients with COVID-19, which can be used to assess the risk of fatal cases of COVID-19[42]. The IL-6 test is not widely available, especially in limited-resource settings. Our meta-analysis showed a relationship between serum ferritin and mortality. Therefore, ferritin can be used as a marker to stratify high-risk hemodialysis patients with COVID-19 with lower cost and wider availability than IL-6.

It should be noted, the level of ferritin in HD patients is influenced by the type of vascular access used by the patients[21]. In COVID-19 case, study by Murt *et al* showed despite the similarity for COVID severity, peak CRP and ferritin levels were higher for patients in whom catheters were used as vascular access and patient with arteriovenous fistula access have better survival[43].

Several limitations of this study should be noted. Given the observational design of the included studies and the retrospective data collection, the possibility that the observed association between each laboratory parameter and the mortality of COVID-19 was affected by bias or confounding factors should still be considered. Assessing the statistical heterogeneity of the included studies is an essential component of interpreting the results of meta-analysis. In the present study, the meta-analysis showed considerable heterogeneity, we attempted to explore sources of statistical heterogeneity by thoroughly examining clinical and methodological heterogeneity across studies and by performing sensitivity analysis. The presence of small sample sizes in several studies included in this meta-analysis has likely contributed to the observed heterogeneity in the overall results.

We also investigated the potential for publication bias in our meta-analysis. Given the significant heterogeneity observed in this meta-analysis and the known limitations of tests for adjusting funnel plot asymmetry, such as the trim-and-fill method, particularly in the presence of substantial between-study heterogeneity, we chose not to conduct a trim-and-fill analysis[44]. Another limitation is small number of the total the total sample size of our meta-analysis due to the limited number of studies that provided data regarding serum ferritin and mortality in regular HD patients with COVID-19 which also contributed to the observed asymmetry in the funnel plot.

Finally, some studies had unclear time points of laboratory collection, this should be taken into consideration when interpreting results. However, we believe that early laboratory testing since the patients were first admitted to the emergency unit can still be used to monitor and anticipate the mortality of COVID-19. Further research can explore a cutoff value for serum ferritin to help physicians predict the mortality of regular hemodialysis patients with COVID-19.

In conclusion, serum ferritin appears to have an association with mortality in regular hemodialysis patients with COVID-19. Our study showed a higher mean of serum ferritin levels in the deceased compared to surviving regular hemodialysis patients with COVID-19.

Conflicts of interest statement

The authors declare that they have no conflict of interest.

Funding

The authors declare that they have no financial support regarding this study.

Authors' contributions

Conception and design of the study by all the authors; acquisition of data by NWAR and YK; analysis and interpretation of data by NWAR and IGRW; drafting and revision of the manuscript by all the authors; and approval of the final version by all the authors.

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