AbdelFattah *et al.*
The Egyptian Journal of Bronchology (2023) 17:45
https://doi.org/10.1186/s43168-023-00218-1

The Egyptian Journal of Bronchology

RESEARCH

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Correlation between the serum level of ferritin and D-dimer and the severity of COVID-19 infection

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Abstract

Background Many laboratory biomarkers were used for diagnosis of COVID-19 infection; however, their accuracy to assess the severity and prognosis are still to be evaluated. This study aims to correlate between the serum ferritin and D-dimer levels and the severity of COVID-19 infection and its outcome.

Results Retrospective data retrieval of 150 confirmed COVID-19 infection patients admitted in Ain Shams University Specialized Hospital El Obour during period between April and July 2020 were studied. Ninety-six were survivors and 54 were non-survivors. The number of co-morbidities, the level of D-dimer and serum ferritin were correlated with ICU admission, need for mechanical ventilation and mortality with *P* value < 0.0001. Serum ferritin and D-dimer levels were significantly correlated with degree of HRCT chest severity with *P* value < 0.0001. The cut-off value of D-dimer for mortality was 700 ng/ml (sensitivity 83.33%, specificity 59.38%), and that for serum ferritin was 300 ng/ml (sensitivity 88.89%, specificity 58.33%), cut-off value of D-dimer for ICU admission was 863 ng/ml and that for serum ferritin was 300 ng/ml, cut-off value of D-dimer for mechanical ventilation was 700 ng/ml, and that for serum ferritin was 600 ng/ml.

Conclusion D-dimer and serum ferritin are important biomarkers in predicting the mortality, ICU admission and need for mechanical ventilation in COVID-19 subjects. Thus helps in early detection of risk of progression and improving outcome. The current study also provides probable cut-off values for both biomarkers above which mortality, ICU admission, and mechanical ventilation need can be expected.

Trial registration ClinicalTrials.gov ID: NCT0567281. Retrospectively registered. 4th January 2023.

https://register.clinicaltrials.gov/prs/app/action/SelectProtocol?sid=S000CT6C&selectaction=Edit&uid=U00056R5&ts=2&cx=-tlu9xu.

Introduction

Risk factors for severe illness I COVID 19 remain uncertain (although older age and comorbidity have emerged as likely important factors) [1, 2].Higher sequential organ failure assessment (SOFA) score and D-dimer > 1 μg/L on admission were associated with higher mortality [3].

While most people with COVID-19 develop only mild (40%) or moderate (40%) disease, approximately 15% develop severe disease that requires oxygen support, and 5% have critical disease with complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multiorgan failure, including acute kidney injury and cardiac injury [3, 4].

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High-resolution CT of the chest is frequently used in the diagnosis of COVID-19 pneumonia, in the course of the disease. High level of D-dimer and ferritin in patients with COVID-19 was associated with HRCT severity score. D-dimer level reflects abnormal coagulation function has been demonstrated to be involved in the disease progression of COVID-19. Ferritin is a mediator for immune dysregulation and is related to disease severity [5, 6].

Aim of the study

To correlate between the serum level of ferritin and D-dimer and the severity and outcome of COVID-19 patients.

Subjects and methods

This was a retrospective cohort study conducted by retrieving data of 500 subjects diagnosed as COVID-19 infection "PCR positive for SARS-CoV2" who were admitted to Ain Shams University Specialized Hospital El Obour designated for COVID-19 patient isolation.in the period from 1st of April 2020 to 31st of July 2020; however, only 150 subjects were fulfilling the inclusion and exclusion criteria and having full patients records.

Inclusion criteria

- Hospitalized isolated subjects with COVID-19 infection confirmed by "polymerase chain reaction (PCR) positive for SARS-CoV2" of all disease severity.

Exclusion criteria

- COVID-19 subjects with any previous history or laboratory investigations altering the serum ferritin level. For example, iron deficiency anemia, defective intestinal absorption, internal bleeding, rheumatoid arthritis, hyperthyroidism, leukemia, Hodgkin's lymphoma, frequent blood transfusions, and advanced liver disease "Child–Pugh score C".
- COVID-19 subjects with any previous history or laboratory investigations altering the serum D-dimer level. For example, known pulmonary embolism, known deep venous thrombosis "DVT", pregnancy, heart failure, trauma, active malignancy, septicemia, disseminated intra-vascular coagulopathy "DIC".
- The patients with any missing studied data were also excluded.

The following data were collected from the studied subjects' files:

- Demographic characteristics (age, sex, smoking status, co-morbidities, and degree of severity of COVID-19 infection according to WHO Clinical management of COVID-19: interim guidance [3].
- *Laboratory investigations* including complete blood picture, iron profile, liver function tests, D-dimer ("using Biomerieux-VIDAS, Serial number IVD 3002806, Manufactured in 2008 1, Marcy l'Étoile, France "Reference range: 0–500 ng/ml") and serum ferritin ("using ABBOT-Architect 1000, Serial number I1SR62514, Manufactured in 2010, Chicago, IL, USA." Reference range: 13–150 ng/ml"
- *Radiological investigations:* high-resolution CT chest (using: Toshiba 16-slice CT scanner, model number: activion 16, Manufactured in 2010, Japan)" severity scoring was done using" 25-point CT severity score considering the extent of anatomic involvement, as follows; the 3 lung lobes on the right and 2 lobes on the left were individually assessed, and percentage involvement of each lobe was noted based on visual assessment. Visual severity scoring of CT chest was classified as Score-1 (< 5% area involved), Score-2 (5–25% area involved), Score-3 (25–50% area involved), Score-4 (50–75% area involved), Score-5 (> 75% area involved), making the total score 25″, as previously described in detail by Sharma et al. 2022 [4].

❖ Study outcomes: survivor or non-survivor, days of hospital stay, need for ICU admission and need for mechanical ventilation.

❖ All patient management were according to Ain Shams University Protocol of COVID-19 in Adults [7].

❖ Ethics approval: study protocol was revised and approved by the institution ethical committee of scientific research, Faculty of Medicine, Ain Shams University (committee's reference number: FMASU MS220/2020). Data were collected anonymously from subjects' records.

Statistical analysis

Data was collected, revised, coded, and entered to the Statistical Package for Social Science (IBM SPSS) version 23 "manufactured in Hong Kong, China". The quantitative data were presented as mean, standard deviations, and ranges when parametric and median, inter-quartile range (IQR) when data found non-parametric. Also, qualitative variables were presented as number and percentages. The comparison between groups regarding qualitative data was done by using *chi-square test* and/or *Fisher's exact test* when the expected count in any cell found less

than 5. The comparison between more than two groups regarding quantitative data and parametric distribution was done by using *one-way ANOVA test* while with non-parametric distribution was done by using *Kruskal–Wallis test*. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the *p* value was considered significant as the following: *P* value > 0.05: non-significant (NS), *P* value < 0.05: significant (S), and *P* value < 0.01: highly significant (HS)).

Receiver operating characteristic curve (ROC) was used to assess the best cut-off point with its sensitivity, specificity, positive predictive value, negative predictive value, and area under curve (AUC) of the studied markers.

Results

Out of 150 patients which constitutes the study population 39, 21, 18, and 72 were diagnosed as mild, moderate, severe, and critical COVID-19 infection, respectively. The cases were classified according to *NIH, COVID-19 treatment guidelines, 2021* [8]. There were 78 male (52%) and 72 female (48%). The mean age of study population was 54.50 ± 18.44 (range 10 to 87) with *P* value < 0.0001.

Comparison between the different degrees of severity of COVID-19 infection and the demographic characteristics and patients' outcomes of the studied subjects are shown in Table 1. There was highly significant difference between the degree of severity of COVID-19 infection and patient age as well as the presence of comorbidities. Older patients with more comorbidities including hypertension and diabetes mellitus were more significantly present in the critical ill and severe groups when compared with those with mild and moderate groups of COVID-19 disease with *P* value < 0.0001. There was highly significant difference between the degree of severity of COVID-19 infection and patients' outcomes as regards mortality, need for ICU admission and need for mechanical ventilation. More morality and need for both ICU stay, and mechanical ventilation were highly significant encountered in the critical ill group when compared with other groups of COVID-19 disease with *P* value < 0.0001.

Critical ill and severe groups of COVID-19 disease had highly significant serum values of D-dimer and ferritin versus mild and moderate groups of COVID-19 disease with *P* value < 0.0001 (Table 2).

There was highly significant difference between median D-dimer and serum ferritin levels and all study outcomes as shown in Tables 3 and 4 with *P* value < 0.0001.

There was highly significant difference between different HRCT chest severity degrees and median D-dimer and serum ferritin levels are seen in Table 5 with higher serum levels of D-dimer and ferritin in higher scores of HRCT chest with *P* value < 0.0001.

The present study shows also that 83.33% of the subjects with D-dimer level above 700 ng/ml were non-survivors, whereas 88.89% of the subjects with serum ferritin level above 300 ng/ml were non-survivors, while 87.04% of the subjects where D-dimer was above 700 ng/ml and serum ferritin was above 300 ng/ml were non-survivors as shown in Fig. 1.

Likewise, this study shows that 76% of the subjects with D-dimer level over 863 ng/ml required ICU admission though 81.33% of the subjects with serum ferritin level over 300 ng/ml required ICU admission and 90.67% of the cases where D-dimer was over 863 ng/ml and serum ferritin was over 300 ng/ml required ICU admission as shown in Fig. 2.

The current study shows also that 83.64% of the subjects with D-dimer level over 700 ng/ml required mechanical ventilation with sensitivity 83.64% and specificity 60%, though 74.55% of the subjects with serum ferritin level over 600 ng/ml required mechanical ventilation with sensitivity 74.55% and specificity 73.68%, while 87.27% of the cases where D-dimer was over 700 ng/ml and serum ferritin was over 600 ng/ml required mechanical ventilation with sensitivity 87.27% and specificity 61.05% as shown in Fig. 3.

Discussion

In this retrospective study, it was found that there was a highly significant correlation between levels of serum ferritin and D-dimer and the severity of COVID-19 infection as regards mortality, severity of HRCT chest affection, need for ICU admission, and for mechanical ventilation.

The methodology of the current study was time bound of retrospective nature similar to other studies in literature conducted to test different laboratory variables of COVID-19 infection [6, 9].

In the current study, the sex distribution was males 78 (52.0%) and females 72 (48.0%) having a non-significant correlation with the severity of COVID-19 infection, which contradicts the results proposed by AbdelGhafaar et al., who conducted a multicentred retrospective study on 3712 Egyptian hospitalized subjects in 6 quarantine hospitals in Egypt in June and July 2020, where male gender was found to be significantly correlated with the increased risk of death among admitted *subjects* [10] and Rosenfeld et al., who conducted a retrospective study on 34,503 COVID-19 in Alaska, Washington, Oregon, Montana, and California in the period between February 28, 2020 and April 27, 2020, found a positive correlation with male gender as well, this could be correlated to having other laboratory abnormalities where serum creatinine

Table 1 Comparison between the different degrees of severity of COVID-19 infection and the demographic characteristics and outcomes

		All patients No. = 150	Mild No. = 39	Moderate No. = 21	Severe No. = 18	Critical No. = 72	Test value	*P* value
Age (years)	Mean ± SD	54.50 ± 18.44	38.13 ± 13.45	49.33 ± 18.08	53.78 ± 16.39	65.06 ± 13.87	29.300 [b]	< 0.0001
	Range	10–87	17–71	10–72	28–82	26–87		
Sex	Female	72	24 (61.5%)	8 (38.1%)	7 (38.9%)	33 (45.8%)	4.423[a]	0.219
	Male	78	15 (38.5%)	13 (61.9%)	11 (61.1%)	39 (54.2%)		
Smoking status	Non-smoker		37 (94.9%)	17 (81.0%)	14 (77.8%)	54 (75.0%)	8.307[a]	0.216
	Current smoker	122(81.3%) 16 (10.7%) 12 (8.0%)	2 (5.1%)	3 (14.3%)	2 (11.1%)	9 (12.5%)		
	Ex-smoker		0 (0.0%)	1 (4.8%)	2 (11.1%)	9 (12.5%)		
Comorbidities	Yes	54 (36%)	3 (7.7%)	5 (23.8%)	8 (44.4%)	38 (52.8%)	24.272[a]	< 0.0001
	Diabetes	30 (20.0%)	2 (5.1%)	1 (4.8%)	3 (16.7%)	24 (33.3%)	16.564[a]	0.001
	Hypertension	33 (22.0%)	2 (5.1%)	2 (9.5%)	5 (27.8%)	24 (33.3%)	14.114[a]	0.003
	IHD	11 (7.3%)	1 (2.6%)	0 (0.0%)	2 (11.1%)	8 (11.1%)	4.857[a]	0.183
	CKD	14 (9.3%)	1 (2.6%)	2 (9.5%)	2 (11.1%)	9 (12.5%)	3.033[a]	0.387
	CLD	7 (4.7%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	6 (8.3%)	5.145[a]	0.161
	AF	4 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (5.6%)	4.452[a]	0.217
	Heart failure	2 (1.3%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0.978[a]	0.807
	ICH	2 (1.3%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (1.4%)	3.252[a]	0.354
	Acute kidney injury	2 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.8%)	2.196[a]	0.533
	Neurological disorders	10 (6.6%)	0 (0.0%)	1 (4.8%)	1 (5.6%)	9 (12.5%)	6.203[a]	0.102
Primary outcome (mortality)	Survivor	96 (64.0%)	39 (100.0%)	21 (100.0%)	18 (100.0%)	18 (25.0%)	91.406 [a]	< 0.0001
	Non-Survivor	54 (36.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	54 (75.0%)		
Days of hospital stay	Range	1–32	8 (4–13)	8 (7–12)	10 (8–16)	8.5 (6–13.5)	4.508 [c]	0.212
			2–30	4–20	3–26	1–32		
Need for ICU admission	Yes	75 (50.0%)	1 (2.6%)	0 (0.0%)	5 (27.8%)	69 (95.8%)	120.158 [a]	< 0.0001
Need for mechanical ventilation	Yes	55 (36.7%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	54 (75.0%)	87.799 [a]	< 0.0001

P value > 0.05 non-significant, *P value < 0.05* significant, *P value < 0.01* highly significant

[a] Chi-square test

[b] One-way ANOVA test

[c] Kruskal-Wallis test, *IHD* Ischemic heart disease, *CKD* Chronic kidney disease, *CLD* Chronic liver disease, *AF* Atrial fibrillation, *ICH* Intra-cranial haemorrhage, *IQR* Interquartile range

Table 2 Comparison between the different degrees of severity of COVID-19 infection and serum values of D-dimer and ferritin

		Mild No. = 39	Moderate No. = 21	Severe No. = 18	Critical No. = 72	Test value [a]	*P* value
D-dimer (ng/ml)	Median (IQR) [b]	275 (150–460)	728 (205–1116)	916 (142–1540)	1883 (924.5–4619.5)	46.707 [a]	< 0.0001
	Range	14–10,000	50–3394	45–10,000	242–10,000		
Serum Ferritin (ng/ml)	Median (IQR) [b]	75 (49–200)	346 (183–1176)	417 (132–900)	742 (427.5–1200)	58.551[a]	< 0.0001
	Range	8–830	13–2000	67–1200	64–120,000		

P value > 0.05 non-significant, *P value < 0.05* significant, *P value < 0.01* highly significant

[a] Kruskal-Wallis test

[b] *IQR* Interquartile range

Table 3 Association between D-dimer serum level and study outcomes

		D-dimer level (ng/ml)		Test value [a]	*P* value
		Median (IQR) [b]	Range		
Mortality	Survivor	501.5 (198.5–1500)	14–10,000	−5.085[a]	< 0.0001
	Non-survivor	1883 (993–4580)	242–10,000		
Need for ICU admission	No	340 (163–863)	14–10,000	−7.174[a]	< 0.0001
	Yes	1936 (993–4659)	242–10,000		
Need for mechanical ventilation	No	500 (198–1500)	14–10,000	−5.375[a]	< 0.0001
	Yes	1901 (993–4659)	242–10,000		

P value > 0.05 non-significant, *P value < 0.05* significant, *P value < 0.01* highly significant

[a] Mann-Whitney test

[b] *IQR* Interquartile range

Table 4 Association between serum ferritin and study outcomes

		Serum ferritin (ng/ml)		Test value[a]	*P* value
		Median (IQR) [b]	Range		
Mortality	Survivor	202.5 (71–815)	8–6625	−5.371[a]	< 0.0001
	Non-Survivor	742 (489–1200)	94–120,000		
Need for ICU admission	No	183 (64–534)	8–2000	−5.913[a]	< 0.0001
	Yes	743 (369–1200)	64–120,000		
Need for mechanical ventilation	No	202 (70–741)	8–6625	−5.725[a]	< 0.0001
	Yes	876 (542–1200)	94–120,000		

P value > 0.05 non-significant, *P value < 0.05* significant, P *value < 0.01* highly significant

[a] Mann-Whitney test

[b] *IQR* Interquartile range

Table 5 Comparison between different HRCT chest severity degrees and serum levels of ferritin and D-dimer

		HRCT chest [c] severity "25-pointscoring system"				Test value[a]	*P* value
		No	Mild	Moderate	Severe		
		No. = 33	No. = 36	No. = 34	No. = 47		
D-dimer (ng/ml)	Median (IQR) [b]	275(150–503)	769.5(195–1752)	1123(602–2416)	2144(713–4659)	35.423	< 0.0001
	Range	14–10,000	45–10,000	120–10,000	100–10,000		
Serum ferritin (ng/ml)	Median (IQR) [b]	103(54–202)	323(74.5–1133.5)	741(460–1200)	703(314–1200)	36.843	< 0.0001
	Range	8–1200	12–12,000	72–6625	64–120,000		

P value > 0.05 non-significant, *P value < 0.05* significant, *P value < 0.01* highly significant

[a] Kruskal-Wallis test

[b] *IQR* = inter-quartile range

[c] *HRCT chest* = high-resolution computed tomography of the chest

and white cell count were found to be more elevated in males than in females [11].

In the current study, there was a highly significant correlation between COVID-19 disease severity and age which is consistent with the findings stated by Zayed et al., who conducted a cross-sectional observational study on 202 COVID-19 subjects in Zagazig University isolation hospitals from the period of March 2020 to June 2021. It was found that the age was a predictor of higher risk of mortality, need for ICU

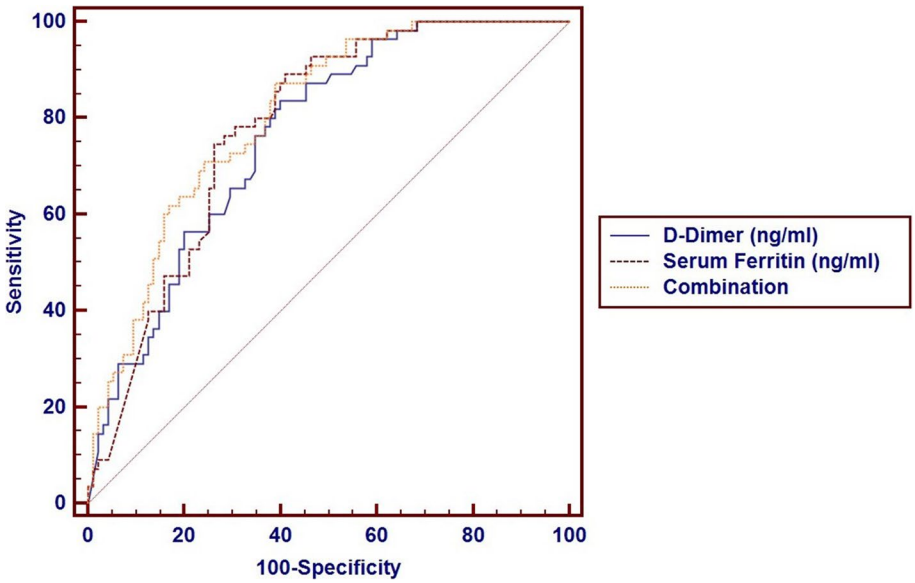

Fig. 1 ROC curve of D-dimer, serum ferritin and combination as a predictor of non-survival

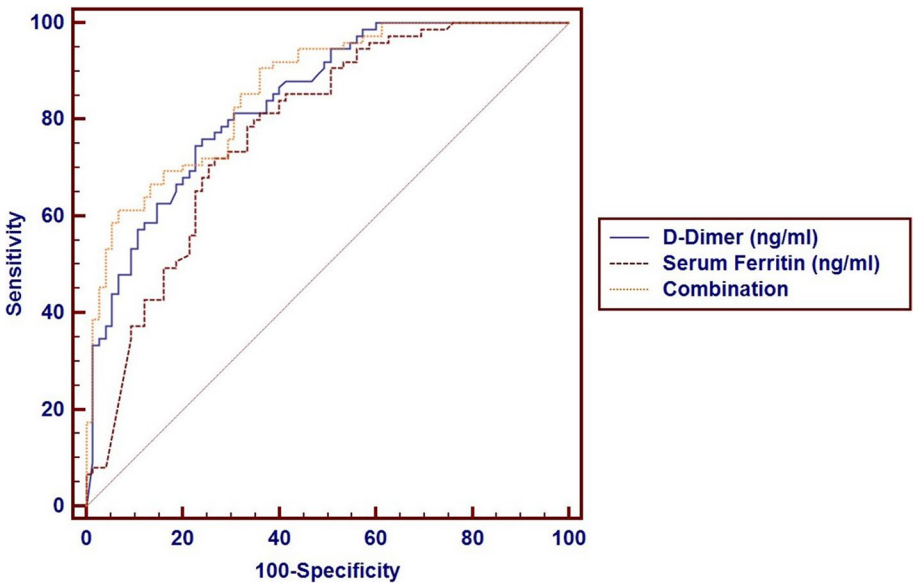

Fig. 2 ROC curve of D-dimer, serum ferritin and combination as a predictor of ICU need

admission and mechanical ventilation in COVID-19 subjects [12].

In the current study, marital status was shown to have a highly significant correlation with the severity of COVID-19 infection which may be due to the burden of domestic responsibilities and delay of seeking medical advice. However the literature correlated it in terms of its psychological impact on the COVID-19 subjects as stated by AboKresha et al.[13] and its effect on quality of life as stated by Purba et al. [14] not in terms of its correlation to the severity of COVID-19 infection which makes this point needs more research.

As regards smoking, there is a controversy whether it is protective or not against COVID-19 infection where smoking is known to increase the risk of infection of both bacterial and viral diseases, such as the common cold, influenza, and tuberculosis, as well as the well-known harmful effect of smoking on the local defence

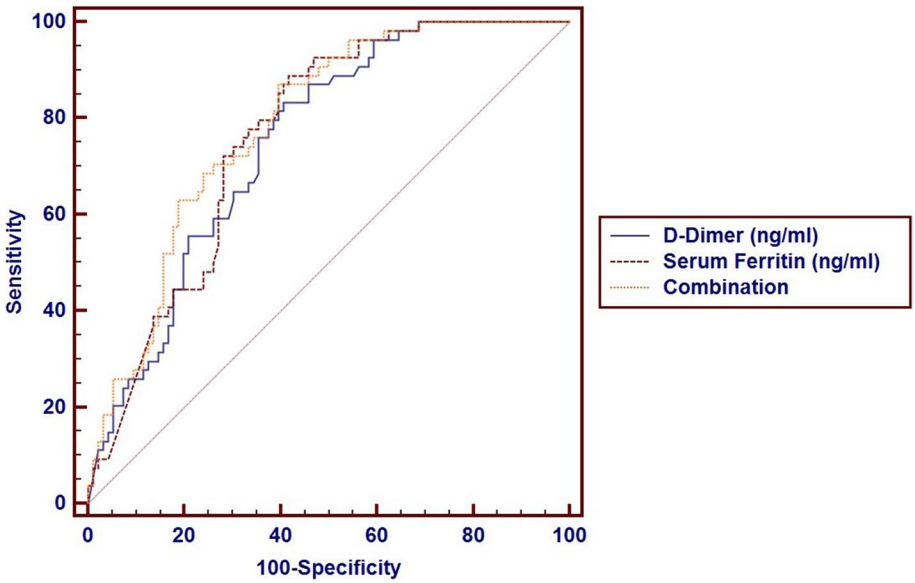

Fig. 3 ROC curve of D-dimer, serum ferritin and combination as a predictor of mechanical ventilation need

mechanism of the respiratory system. However some observational studies found that it was not associated with SARS CoV-2 infection which contradicts earlier studies [15] as well which found that smokers are more vulnerable to respiratory infections in particular [16].

In the current study, there was a non-significant correlation between severity of COVID-19 infection and smoking status which contradicts with previous systematic review and meta-analysis of 47 studies by Reddy et al. They reported that subjects with a smoking history had a significantly increased risk of severe COVID-19 as regards mortality and disease progression [17]. This controversy may be due to having variable sample sizes as well as the great need for knowledge analysis regarding COVID-19.

In the current study, there was a highly significant correlation between severity of COVID-19 infection and the presence of co-morbidities especially diabetes and hypertension. Similar findings were reported by Ji et al. whom conducted a Korean nationwide retrospective case–control study of 219,961 COVID-19 subjects**,** where co-morbidities especially diabetes and hypertension highly significantly affected the severity of COVID-19 infection [18].

There was a highly significant correlation between severity of COVID-19 infection and disease mortality. This was in agreement with several Egyptian and international studies as well [19–21].

In this study, a positive correlation was found between severity of COVID-19 infection, days of hospital stay [22], the need for ICU admission, and mechanical ventilation which seems a logic finding.

The current study shows that the number of comorbidities has a positive correlation with the severity of COVID-19 infection which is consistent with what was reported by Djaharuddin et al., whom conducted a retrospective descriptive study on 454 COVID-19 cases and found that hypertension, cardiovascular disease, and diabetes were the most common cause of death in COVID-19 subjects and that more than half of the subjects had two or more comorbidities [23, 24]. However, it had no correlation with days of hospital stay, which may be due to having different criteria for admission and discharge. The literature supporting or contradicting this point are deficient.

D-dimer is one of the fragments produced when plasmin cleaves fibrin to break down clots. The assays are routinely used as part of a diagnostic algorithm to exclude the diagnosis of thrombosis. In any case, any pathologic or non-pathologic process that increases fibrin production or breakdown also increases plasma D-dimer levels. COVID-19 inflammatory process subsequently activates the coagulation process which probably causes elevated D-dimer levels [25].

Despite the presence of many papers reporting the association between D-dimer and the severity of COVID-19 yet it was not fully studied and seems unclear.

In the current study, there was a positive correlation between severity of COVID-19 infection and the level of D-dimer where significantly higher levels were found

in those with critical illness which supports the application of D-dimer in COVID-19 as a prognostic marker for mortality and disease progression not just as a diagnostic tool for thromboembolism**.** This was similar to what was reported by Yao et al., who conducted a retrospective analysis of the clinical, laboratory, and radiological characteristics of 248 consecutive cases of COVID-19 in Wuhan, China, where they found that D-dimer level correlates with disease severity and was a reliable prognostic marker for in-hospital mortality in subjects admitted for COVID-19 [25]. Varikasuvu et al.reported the presence of a strong relationship between subjects with higher D-dimer and the risk of overall disease progression through a systematic review and meta-analysis of 100 studies [26]. Also, Yameny reported that markedly elevated D-dimer levels were observed in COVID-19 non-survivors [27].

Ferritin is a key mediator of immune dysregulation, especially under extreme hyper-ferritinemia, via direct immune-suppressive and pro-inflammatory effects, contributing to the cytokine storm. Fatal outcomes by COVID-19 are accompanied by cytokine storm syndrome, thereby it has been suggested that disease severity is dependent of the cytokine storm syndrome which supports the hypothesis that ferritin levels might be a crucial factor influencing the severity of COVID-19 [28].

In the current study, there was a positive correlation between levels of serum ferritin and severity of COVID-19 infection. Similar experiences were also recorded by international studies including Zhou B et al. through a single centre observational analysis of 20 in-hospital severe subjects with COVID-19, the results showed that the analysed inflammatory markers including ferritin were markedly increased in very severe compared with severe COVID-19 [29]. Vargas-Vargus et al. studied 20 subjects with severe and very severe COVID-19 exhibited increased serum ferritin level, where serum ferritin in the very severe COVID-19 group was significantly higher than in the severe COVID-19 group which supports its correlation with disease severity [28].

In agreement with this, Zhou F et al. conducted a retrospective, multicentre cohort study including 20 adult in subjects which revealed that subjects who died by COVID-19 had high ferritin levels upon hospital admission and throughout the hospital stay [30].

In the current study, there was no correlation between either D-dimer and serum ferritin and days of hospital stay. In contrast, Thiruvengadam et al. found contradictory results to current study. In whom they conducted a retrospective study on 730 COVID-19 subjects, they found that elevated D-dimer and ferritin values were among the factors associated with the longer length of hospital stay [31]. This may be due to the difference in the size and the demographic characteristics of the studied population than present study and the difference of the local guidelines of hospital admission.

In the current study, D-dimer had a highly positive correlation with the mortality (primary outcome). This was in agreement with Poudel et al. whom conducted a retrospective study on 182 COVID-19 subjects studying different clinical and laboratory parameters, including D-dimer [32], Soni et al., whom retrospectively analysed data of 483 COVID-19 subjects [33], Khamiss et al., whom conducted retrospective study of 333 COVID-19 subjects as regards clinical and laboratory data including D-dimer [34], and AbdelGhaffar et al., whom conducted a retrospective analysis of 3712 COVID-19 subjects' data, they all proved that among the coagulation parameters, D-dimer value on admission and during hospital stay is an accurate biomarker for predicting mortality in subjects with COVID-19 [10].

In the current study, D-dimer was found to have a positive correlation with the need for ICU admission which is consistent with Bansal et al., who conducted a systematic review and meta-analysis of the published literature evaluating D-dimer levels in SARS-COV-2 infected subjects and their outcomes in which they found that SARS-CoV-2 infected subjects with elevated D-dimers had worse clinical outcomes defined as mortality, ICU admission, or ARDS [35].

In the current study, there was a positive correlation between D-dimer and need for mechanical ventilation which is similar to what was reported by Li et al., whom conducted a retrospective study on 1643 COVID-19 subjects, where a higher percentage of those whom required oxygen support including low-flow nasal cannula, non-invasive ventilation or high-flow nasal cannula, invasive mechanical ventilation, and ECMO (extracorporeal membrane oxygenation) had increased D-dimer levels [36].

In the current study, serum ferritin had a positive correlation with the mortality, which was the same as proved by Alroomi et al., whom conducted a retrospective study on 595 COVID-19 subjects, where higher levels of serum ferritin were found to be an independent predictor of mortality [37].

A positive correlation was found as well in the current study between serum ferritin level and the need for ICU admission and mechanical ventilation. This is supported by the results obtained by Kaushal et al., whom conducted a systematic review and meta-analysis of 163 studies to evaluate the association between serum ferritin and severity and outcome of COVID-19. They reported that subjects requiring ICU had a higher serum Ferritin level than subjects whom did not require the same and that there was an association of higher level

of serum Ferritin and requirement of mechanical ventilation [38]. In addition to this, Elsharawy et al., whom conducted a retrospective study on 170 COVID-19 cases admitted at Tanta University and Kafr El-sheikh University isolation hospitals, they reported that serum ferritin was associated with disease severity and prediction of ICU admission [39].

In the current study, there was a positive correlation between levels of serum ferritin and D-dimer and the degree of severity of HRCT chest. Yilmaz et al., whom conducted a single-centred, retrospective, descriptive and observational study including 130 COVID-19 subjects, reported that serum ferritin and D-dimer levels were observed to be high in the CT-positive group and have positive correlation with CT severity [40].

In the current study, the estimated cut-off value of D-dimer for mortality was above 700 ng/ml with sensitivity 83.33%, while Poudel et al., found that 1.5 µg/ml is the optimal cut-off value of admission D-dimer for predicting mortality in COVID-19 subjects [32]. Another study by Li et al. whom conducted a meta-analysis on COVID-19 subjects, reported D-dimer value of 1 µg/ml as a cut-off value for mortality [41].

In the current study, the estimated cut-off value of serum ferritin level for mortality was above 300 ng/ml with sensitivity of 88.89%, while Alroomi et al., found that the higher mortality rate was among subjects having serum ferritin levels > 1000 [37], on the other hand, Zhou B et al. reported a cut-off value of more than 300 ng/ml for mortality [29] and Ahmed et al. who conducted a retrospective study on 157 COVID-19 subjects, found that the optimal cut-off value for prediction of mortality was 574.5 ng/ml [42], this discrepancy may be due to the difference in the study population as regards their size and site.

In this study, the estimated cut-off value of D-dimer level above which the subjects needed ICU admission was 863 ng/ml with sensitivity about 76%, while Hashem et al. stated that D-dimer level above 900 ng/L the best value to predict ICU admission for COVID-19 subjects with sensitivity = 72.4% [43].

In the current study, 81.33% of the subjects with serum ferritin level above 300 ng/ml needed ICU admission, this is similar to what was reported by Elsharawy et al. where the cut-off value of serum ferritin was above 300 ng/ml [39].

In the current study, the estimated cut-off value for mechanical ventilation need was above 700 ng/ml for D-dimer with sensitivity of about 83.64%, meanwhile it was above 600 ng/ml for serum ferritin with sensitivity of 74.55%. However different values were stated by Qeadan et al., whom conducted a retrospective cohort study of 52,411 COVID-19 subjects, where the optimal cut-off values for mechanical ventilation were 502 ng/mL as regards serum Ferritin and 2.0 mg/L "200 ng/ml" as regards D-dimer [44]. This difference may be due to having different population size which makes this point need further research.

The study has certain limitations. Being of retrospective nature, thus it carries inherited drawbacks of this type including data collection, data entry and data quality assurance, were not planned ahead of time as well as exclusion of appreciable number of cases because of incomplete data. The sample size was affected by nature of study being retrospective and time-bound. These limitations may have influenced study results.

Conclusion

This study spots the importance of the use of inflammatory markers such as D-dimer and serum ferritin in predicting the outcome of COVID-19 subjects, as they have a strong relation with disease mortality, ICU admission, and need for mechanical ventilation, which helps in early detection of case risk of progression and consequently improving outcome. In addition, the current study also provides probable cut-off values for both serum ferritin and D-dimer above which mortality, ICU admission and mechanical ventilation need can be expected which needs further evaluation.

Abbreviations

COVID-19	Coronavirus disease of 2019
M.B.B.Ch.	Bachelor of Medicine, Bachelor of Surgery
M.D.	Medicinae Doctor (Doctor of Medicine)
ICU	Intensive care unit
HRCT	High-resolution computerized tomography
Ng/ml	Nanogram per millilitre
CDC	Centre of disease control and prevention
WHO	World Health Organization
ARDS	Acute respiratory distress syndrome
PCR	Polymerase chain reaction
SARS-CoV2	Severe acute respiratory syndrome coronavirus 2
VIDAS	VITEK ImmunoDiagnostic Assay System
IVD	In-vitro diagnostic device
CT	Computerized tomography
DVT	Deep venous thrombosis
DIC	Disseminated intra-vascular coagulopathy
IBM SPSS	International Business Machines Corporations-Statistical Package for Social Science
IQR	Inter-quartile range
ANOVA	Analysis of variance
P value	Probability value
NS	Non-significant
S	Significant
HS	Highly significant
ECMO	Extracorporeal membrane oxygenation
µg/ml	Microgram per milliliter
ng/L	Nanogram per liter
IHD	Ischemic heart disease
AF	Atrial fibrillation
AUC	Area under curve
PPV	Positive predictive value
NPV	Negative predictive value

Acknowledgements
Not applicable.

Authors' contributions
All authors have read and approved the final manuscript.

Funding
No funding was used in the current research.

Availability of data and materials
Tables included.

Declarations

Ethics approval and consent to participate
Study protocol was revised and approved by the institution ethical committee of scientific research, Faculty of Medicine, Ain Shams University (committee's reference number: FMASU MS220/2020). Data were collected anonymously from subjects' records.
Trial registration: ClinicalTrials.gov ID: NCT0567281. Retrospectively registered. 4th Jan 2023.
https://register.clinicaltrials.gov/prs/app/action/SelectProtocol?sid=S000CT6C&selectaction=Edit&uid=U00056R5&ts=2&cx=-tlu9xu.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 13 February 2023 Accepted: 7 August 2023
Published online: 30 August 2023

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