The Egyptian Journal of Bronchology

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Study of CRP, ferritin, and D-dimer in COVID-19 RICU patients as per HRCT severity in assiut university hospitals

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Abstract

Background Inflammatory markers were found to be elevated in patients with coronavirus disease (COVID-19). C-reactive protein (CRP), serum ferritin, and D-dimer levels may predict morbidity and mortality in (COVID-19) patients. Radiology plays a key role in the diagnosis, management, and follow-up of this disease. This study aimed to describe the radiological features of (COVID-19) infection, measure C-reactive protein (CRP), D-dimer, and ferritin levels and to correlate them with patient's outcome and to consider them as predictors of morbidity and mortality in (COVID-19) patients.

Methods This prospective cross-sectional analytic study had been done on 159 patients aged ≥ 18 years old, admitted at Assiut University Hospital RICU from November 2021 to November 2022, diagnosed as COVID-19 by positive RT-PCR. All patients were categorized on bases of HRCT chest disease reporting and data system (CO-RADS) scoring system into non-severe (CO-RADS 1,2,3) and severe (CO-RADS 4,5) groups. Inflammatory markers such as CRP, ferritin, and D-dimer were measured. Age, sex, comorbidities, need to mechanical ventilation MV, and mortality rate were reported. Correlation between HRCT(CO-RADS) score, inflammatory markers, and patient's outcome was assessed.

Results Higher CRP and serum ferritin levels, lower lymphocytic count, and higher frequency of need for mechanical ventilation were significantly greater in the severe group ($P < 0.0001$). Predictors of morbidity and mortality were CRP ≥ 133 mg/dl, DM, presence of chronic chest disease ($P < 0.0001$). A higher mortality rate was in patients of the severe group (65%) versus (9%) in the non-severe group ($P < 0.0001$).

Conclusions HRCT scan and measurement of CRP and ferritin plasma levels can be considered significant predictors for future prognosis and can early identify patients at risk of death and need for MV. Male gender, presence of DM, and chronic chest diseases are risk factors for severe illness.

Keywords COVID-19, CRP, Ferritin, D-dimer, ICU

Introduction

COVID-19 is the illness produced by the coronavirus known as SARSCoV-2. WHO initially gained awareness of this virus on December 31, 2019, upon getting an alert about a group of instances of "viral pneumonia" in China [1, 2].

Recent studies have investigated the importance of chest HRCT in COVID-19 patients who have the virus. According to previous literature, a sensitivity of about 98% is present for diagnosis and monitoring the progression of the disease and efficacy of treatment. HRCT can categorize stage and severity of COVID19 pneumonia [3, 4].

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It has been observed that in many situations RT-PCR test is negative or inconclusive, but the HRCT in such cases is useful and conclusive [5].

Patients with COVID-19 frequently exhibit elevated concentrations of inflammatory markers, like D-dimer, CRP, ferritin, lactate dehydrogenase (LDH), and IL-6. The distribution features of CRP varied across COVID-19 patients, with variances observed in different age groups, clinical types, and outcomes. [6].

Individuals with severe forms of COVID-19 exhibited elevated levels of inflammatory cytokines, which are correlated to lung inflammations and end with multiple organ failure [7, 8].

The exact causes for the extensive presence of inflammatory cytokines remain uncertain; however, they may have a significant impact on cell death linked to organ damage [9, 10].

Multiple studies conducted in Wuhan revealed that COVID-19 individuals with increased levels of D-dimer exhibited a greater risk of mortality. However, the impact of anticoagulation on concentrations of D-dimer among COVID-19 individuals is not well understood. Typically, patients who receive anticoagulation treatment tend to have very low D-dimer levels [11].

While various research has indicated a potential link between elevated levels of ferritin, CRP, and D-Dimer with the presence of severe disease, the findings across these studies are not completely uniform. Currently, it remains uncertain if there is a substantial difference in inflammatory markers between people with severe COVID-19 contrasted to individuals with mild disease [12].

The purpose of this work was to describe the radiological HRCT features of (COVID-19) infection, measure C-reactive protein (CRP), D-dimer, and ferritin levels and to correlate it with patient's outcome and to consider them as predictors of morbidity and mortality in (COVID-19) patients.

Patients and methods

Ethical approval

This study was approved by the Ethics committee of the Faculty of Medicine, Assiut University (IRB no.17101508). A written informed consent form was permanently incorporated into the participants' study records and was stored in the same manner as other records. This work had been conducted in compliance with the recommendations clearly defined in the Declaration of Helsinki. The study was registered in clinicaltrials.gov with the number (NCT05102695).

We excluded from the study patients diagnosed as COVID-19 but not admitted to RICU or were discharged from emergency department ER for home isolation.

We included in this study patients above 18 years old, diagnosed as COVID-19 by RT-PCR and admitted to RICU.

Each participant had been exposed to complete taking of history, clinical examinations, patients' outcome, need for mechanical ventilation MV, laboratory tests (serum ferritin, CRP, D-dimer and arterial blood gases (ABG)), and HRCT chest.

Arterial blood gas

Blood samples were collected under complete sterile conditions using IL-GEM-Premier3000 device.

Measurement of serum CRP, ferritin and plasma D-dimer levels

We utilized the Cobas® 6000 modular (c501 and e601) Biochemistry and Immunoassay analyzer to measure the levels of serum ferritin and CRP. The reagent kits utilized were from Roche Diagnostics, a company based in Basel, Switzerland. The serum D-dimer was measured using the STAR Max® hemostasisanalyzer from Diagnostica Stago Inc., located in Asnières-sur-Seine, France. The measurement was performed using an immune-turbidimetric assay.

The BRI for it was deemed to be less than 0.5 μg/mL. The assessment of quality control was conducted employing the internal quality control material "PreciControl" supplied by Cobas, Roche Diagnostics, based in Basel, Switzerland.

Measurement of PCR level

PCR-Q96 Series machine was used for analysis of the PCR Swabs taken from each patient. A thin and flexible elongated nasal swab (specifically a nasopharyngeal swab) was put into the patient's nostril, with a cotton tip at the end. Subsequently, another stick was used to brush the swab down the posterior part of the patient's throat, in order to get a sample of mucus. To get an adequate amount of mucus for the test, swabbing might be performed in both nostrils during the nasal sample collection. The swab was left in position momentarily before being delicately spun while being withdrawn. The specimen was securely enclosed within a tube and delivered to a laboratory for examination.

Assessment of Covid-19 severity by HRCT chest and CO-RADS Scoring classification

HRCT chest was done to all patients using GE Scanner 64 slice machine. All patients were then categorized on bases of HRCT chest disease reporting and data system (CO-RADS) scoring system into non-severe (CO-RADS 1, 2, and 3) and severe (CO-RADS 4 and 5) groups.

CORADS (COVID-19 reporting and data system)

The CORADS system is designed to aid radiologists and healthcare professionals in assessing the likelihood of COVID-19 infection based on findings from chest CT scans. It assigns a score from 1 to 5, with each score indicating the probability of COVID-19 infection.

Non-severe COVID-19

CORADS 1 or 2

- No abnormalities or findings not suggestive of COVID-19.
- Patients are unlikely to have COVID-19; usually managed outpatient.

CORADS 3

- Indeterminate findings but typically without significant respiratory symptoms or lung involvement.
- These patients may require further testing or monitoring but are not classified as severe.

Severe COVID-19

CORADS 4 (with significant symptoms)

- Likely COVID-19 with moderate to severe respiratory symptoms.
- Significant lung involvement on HRCT (e.g., more than 50% lung involvement or severe consolidations).

CORADS 5

- Highly likely COVID-19 with typical imaging findings for pneumonia.
- Patients may exhibit severe respiratory distress, requiring oxygen supplementation or mechanical ventilation.
- This classification helps in quickly identifying which patients may require more intensive monitoring or treatment [13].
- Correlation between HRCT(CO-RADS) score, inflammatory markers, and patient's outcome was assessed.

Statistical analysis

Statistical Analysis had been conducted employing (SPSS-Version 20) software. All data was displayed as means and frequencies. Clinical characteristics were compared through student test for continuous variables for two groups. Proportions had been contrasted with Chi-square tests. Graphics had been conducted employing Microsoft Excel. *P* value was considered significant if <0.05.

We gathered data on CRP, ferritin, and D-dimer levels and the corresponding mortality outcomes from study population and then identified the optimal cut-off by using Youden's Index, i.e., Youden's Index = Sensitivity + Specificity − 1, then identified the point on the receiver operating characteristic (ROC) curve where this index is maximized. The AUC is then derived from the (ROC) curve. The AUC can be calculated using statistical software SPSS, which provides a numerical value based on the ROC curve.

Results

Patients were categorized into two groups according to HRCT chest (CORADS) severity scoring system: non-severe group (CORADS 1, 2, and 3) and severe group (CORADS 4 and 5). A total of 115 patients were included in the severe group and 44 patients in the non-severe group. No significant difference between both groups was found as regards gender, residence, smoking, and comorbidities (HTN, CVS, hepatic affection, and presence of malignancy). Age, DM, and chronic chest disease were significantly greater among severe group contrasted to non-severe group ($P<0.05$). In Table 1, at presentation, the severe group was more tachycardic, tachypnic, and hypotensive as compared to the non-severe group. In Table 2, on laboratory assessment, higher CRP and ferritin levels, lower lymphocytic count, and more desaturation were significantly found among the severe group ($P<0.05$). In Table 3, need for mechanical ventilation and mortality rate were higher among the severe group ($P<0.001$). In Table 4, at cut-off > 150 mg/dl, baseline CRP had 63% overall accuracy in prediction of mortality among the studied subjects with area under curve that was 0.674. Meanwhile, baseline D-dimer values had 67.7% overall accuracy in prediction of mortality among the studied with area under curve that was 0.706. Figure 1

Discussion

In December 2019, Chinese scientists first identified SARS-CoV-2 as the etiology of COVID-19 disease [14]. At first, COVID-19 was classified as a respiratory illness, with pneumonia considered the prevailing and most fatal consequence. However, SARS-CoV-2

Table 1 Baseline data and comorbidities of the studied patients based on HRCT CORADS classification

		Non-severe group ($n=44$)	Severe group ($n=115$)	*P*
Age (years)		51.93 ± 14.75	63.54 ± 16.32	**< 0.001***
Sex	**Male**	25 (56.8%)	65 (56.5%)	0.55
	Female	19 (43.2%)	50 (43.5%)	
Residence	**Rural**	25 (56.8%)	62 (53.9%)	0.44
	Urban	19 (43.2%)	53 (46.1%)	
Smoking	**Cigarette**	18 (40.9%)	44 (38.3%)	0.44
	Goza	12 (27.3%)	33 (28.7%)	0.51
Comorbidities	**DM**	16 (36.4%)	78 (67.8%)	**< 0.001***
	HTN	13 (29.5%)	37 (32.2%)	0.45
	IHD	14 (31.8%)	45 (39.1%)	0.25
	CVS	5 (11.4%)	19 (16.5%)	0.29
	CKD	8 (18.2%)	25 (21.2%)	0.39
	Chronic Chest disease	5 (11.4%)	45 (39.1%)	**< 0.001**
	Liver disease	4 (9.1%)	8 (7%)	0.43
	Malignancy	1 (2.3%)	6 (5.2%)	0.37

Data are presented as mean ± SD or frequency (%)

DM Diabetes mellitus, *COPD* Chronic obstructive pulmonary disease, *HTN* hypertension, *CVS* Cerebrovascular stroke, *IHD* Ischemic heart disease, *CKD* Chronic kidney disease

*Significant *p* value < 0.05

Table 2 Clinical data at presentation of the studied patients based on HRCT CORADS classification

	Non-severe group ($n=44$)	Severe group ($n=115$)	*P*
Body ache	44 (100%)	113 (98.3%)	0.52
Fever	25 (56.8%)	80 (69.6%)	0.09
Cough	40 (90.9%)	112 (97.4%)	0.34
Dyspnea	43 (97.7%)	113 (98.3%)	0.62
Loss of smell/taste	24 (54.5%)	67 (58.3%)	0.40
Diarrhea	22 (50%)	62 (53.9%)	0.39
Abdominal pain	22 (50%)	53 (46.1%)	0.40
Vomiting	23 (52.3%)	59 (51.3%)	0.52
Temperature (°C)	37.53 ± 0.79	37.67 ± 0.64	0.15
SBP (mmHg)	123.87 ± 21.21	115.48 ± 25.46	**< 0.001***
Heart rate (b/m)	93.65 ± 15.35	100.53 ± 20.57	**< 0.001***
DBP (mmHg)	77.89 ± 12.34	71.44 ± 16.97	**< 0.001***
RR (cycle/m)	28.93 ± 6.58	34.17 ± 7.75	**< 0.001***

Data are presented as mean ± SD or frequency (%)

DBP Diastolic blood pressure, *RR* Respiratory rate, *SBP* Systolic blood pressure

*Significant *p* value < 0.05

had been revealed to produce an unregulated immune responses which leads to various complications including thrombosis, damage to tissues, ARDS, and MODS [15]; Therefore, COVID-19 should not only be considered a respiratory disease but also as a possible multisystem disease [16].

In this study, we classified the studied patients radiologically according to HRCT CORADS into two groups non-severe group (CORADS 1, 2, and 3) and severe group (CORADS 4 and 5).

Some studies found a significant association between computed tomography (CT) severity, gender, and age with the treatment outcome among COVID-19-infected patients admitted to the hospital [17].

The severity and mortality of COVID-19 infections are influenced by factors such as age, gender, and biomarkers indicated by CT severity scores [18].

In this study, as regard comorbidities, significantly higher DM (67.8% vs. 36.4%; $p<0.001$) and chronic chest disease (39.1% vs. 11.4%; $p<0.001$) among severe group was found. Hypertension as recorded was (29.5%; 32.2%) in non-severe group and severe group respectively. CVS was (11.4%; 16.5%) in non-severe group and severe group correspondingly. CKD was (18.2%; 21.2%) in non-severe group and severe group respectively. In accordance, Abdelfattah et al. [19] reported that a strong association existed among the COVID-19 infection severity and the prevalence of co-morbidities, particularly systemic HTN and DM. Ji et al. [20] also observed similar findings. A countrywide retrospective case–control research was undertaken in South Korea, involving 219,961 participants with COVID-19. The work found that comorbidities, particularly DM and HTN, had a substantial impact on the COVID-19 infection severity. According to Khadija et al. [21], 32% of individuals with DM had

Table 3 Arterial blood gases and laboratory data of the studied patients based on HRCT CORADS classification

	Non-severe group ($n=44$)	Severe group ($n=115$)	*P*
ABG			
pH°	7.46 ± 0.07	7.43 ± 0.11	**0.03***
PCO_2 (mmHg)	35.03 ± 12.30	33.21 ± 15.99	0.38
PO_2 (mmHg)	47.65 ± 13.81	40.97 ± 12.45	**< 0.001***
Lactate (mmol/l)	1.85 ± 1.23	2.98 ± 2.55	**< 0.001***
HCO_3 (mmol/l)	24.64 ± 6.86	21.72 ± 7.82	**< 0.001***
Base deficit (mmol/l)	2.96 ± 0.87	2.17 ± 1.19	0.25
Oxygen saturation (%)	81.42 ± 13.81	72.58 ± 17.41	**< 0.001***
Laboratory data			
Leucocytes (10^3/ul)	9.48 ± 5.31	12.01 ± 6.45	**< 0.001***
Neutrophils (10^3/ul)	7.56 ± 5.14	10.26 ± 5.82	**< 0.001***
Lymphocyte (10^3/ul)	1.25 ± 0.75	0.81 ± 0.61	**< 0.001***
Hemoglobin (g/dl)	12.69 ± 2.22	12.15 ± 2.65	0.07
Platelets (10^3/ul)	256.79 ± 113.26	254.14 ± 118.91	0.27
INR	1.10 ± 0.21	1.27 ± 0.73	**< 0.001***
Creatinine (mmol/l)	121.94 ± 24.80	178.25 ± 88.87	**< 0.001***
Urea (mmol/l)	9.94 ± 7.48	16.94 ± 9.65	**< 0.001***
Potassium (mmol/l)	4.14 ± 0.74	4.26 ± 0.76	0.20
Sodium (mmol/l)	136.68 ± 5.17	138.23 ± 5.65	0.74
Albumin (mg/dl)	35.10 ± 5.73	32.97 ± 5.33	**< 0.001***
Bilirubin (umol/l)	9.20 ± 3.45	9.82 ± 2.83	0.56
ALT (u/L)	44.09 ± 11.34	54.83 ± 8.98	0.20
AST (u/L)	45.96 ± 9.45	80.23 ± 32.23	**< 0.001***
ALP (u/L)	101.77 ± 63.44	114.45 ± 83.87	0.81
CRP (mg/dl)	89.36 ± 16.56	142.87 ± 25.57	**< 0.001***
Ferritin (ng/ml)	612.34 ± 34.76	1116.87 ± 123.45	**< 0.001***
D-dimer (mg/l)	2.30 ± 0.48	3.49 ± 0.35	0.06

Data are presented as mean ± SD

ABG Arterial blood gases, *INR* International randomized ratio, *AST* Aspartate transaminase, *CRP* Creactive protein, *ALT* Alanine transaminase, *ALP* Alkaline phosphatase

*Significant *p* value < 0.05

Table 4 Need for mechanical ventilation and mortality rate of the studied patients based on HRCT CORADS classification

		Non-severe group ($n=44$)	Severe group ($n=115$)	P
Venturi mask		41 (93.2%)	41 (35.7%)	**< 0.001***
Nasal canula		14 (31.8%)	39 (33.9%)	0.47
Need for NIV		17 (38.6%)	47 (40.9%)	0.40
Need for MV		3 (6.8%)	76 (66.1%)	**< 0.001***
Outcome	**Survived**	40 (90.9%)	40 (34.8%)	**< 0.001***
	Not survived	4 (9.1%)	75 (65.2%)	

Data are presented as mean ± SD or frequency (%)

NIV Non-invasive ventilation, *MV* Mechanical ventilation

*Significant *p* value < 0.05

HTN, and 9.2% had underlying ischemic cardiac disease. Both of these conditions are known to be risk factors for negative outcomes among individuals with COVID infections.

In the present study, it was found that lymphocytic count was significantly lower among patients with severe group. Also, severe groups exhibited significantly greater serum CRP levels and serum ferritin levels, while no statistically significant variation existed as regards levels of D-dimer among non-severe and severe groups of patients. This agrees with Abdelfattah et al. [19] who reported that a strong connection was seen between serum ferritin and D-dimer and the COVID-19 infection severity. Furthermore, Elsharawy et al. [22] found a correlation between serum ferritin levels and both the severity

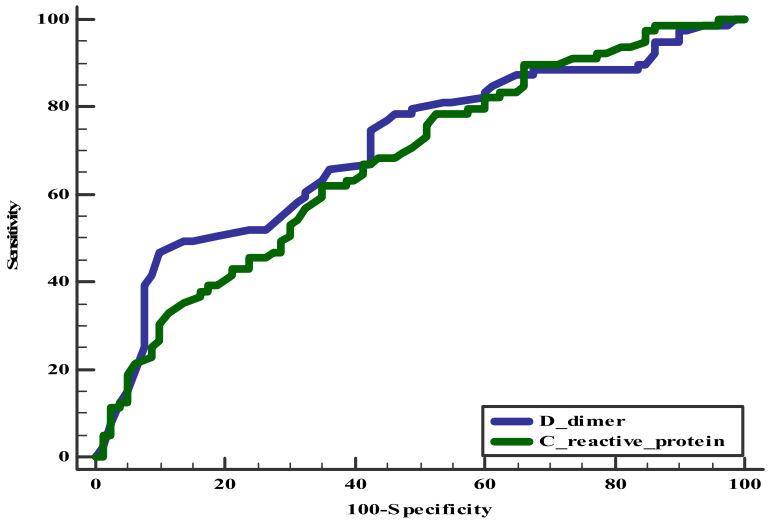

Fig. 1 Accuracy of C-reactive protein and D-dimer in prediction of mortality

of the illness and the ability to predict admission to the ICU. This was in opposition to the findings published by Yao et al. [23]. The study discovered a significant association among level of D-dimer and the severity of the illness. Furthermore, they observed that D-dimer level served as a dependable prognostic marker for predicting in-hospital mortality in individuals admitted for COVID-19. This was in contrast with what was reported by Yao et al. [23] that 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.

In this study, it was found that frequency of need for MV was significantly higher among patients with severe disease (66.1% vs. 6.8%; $p<0.001$), while venture mask was the method of correction of desaturation among non-severe group (93.2% vs. 35.7%; $p<0.001$). In accordance, Abdelfattah al [19]. reported that a positive correlation was found between severity of COVID-19 infection, days of hospital stay, the need for ICU admission, and mechanical ventilation which seems a logic finding.

Higher levels of serum CRP are associated with higher mortality in people with severe COVID-19 disease [23]. more specifically, CRP values above 77.35 mg/L [24]. Davoudi et al. [25] reported that, although the level of CRP was higher in non-survived patients, this difference was not statistically significant. This is the same as proved by Alroomi et al. [26] conducted a retrospective study on 595 COVID-19 subjects, where higher levels of serum ferritin were found to be an independent predictor of mortality.

Blood picture of patients with COVID-19 characterized by normal or low count of WBCs and decreased level of lymphocytes. Increased levels of WBCs and neutrophils were found in 68% and 72% of patients [27]. Petrilli et al. [28] reported striking findings regarding the predictive value of inflammatory markers to distinguish future critical from non-critical illness.

In the present study, at cut-off > 133 mg/dl, baseline serum CRP level had 65.7% overall accuracy in prediction of severe disease among the studied with area under curve that was 0.673. Ahnachet al. [29] confirmed that the CRP was a robust predictor of adverse disease outcome. CRP was also an independent discriminator of severe/critical illness on admission in comparison with other biological factors. These results were in agreement with similar report of Luo et al. [30] found an AUC of CRP for discriminating disease severity on admission at 0.783. With a cut-off value of 41.3, CRP exhibited similar results of our study with sensitivity of 65%, specificity of 83.7%, PPV of 81.6%, and NPV of 68.2%.

In this study, it was found that predictors for severe disease among the studied patients were DM (odd's ratio = 3.45), chronic chest disease (odd's ratio = 2.22), and CRP (odd's ratio = 2.19). Similarly, Wang et al. [31] and Wu et al. [32] reported a significant association of the COVID-19 severity with diabetes.

In our study, it was found that predictors for mortality among the studied patients were age (odd's ratio = 1.78), DM (odd's ratio = 2.89), chronic chest disease (odd's ratio = 3.01), serum albumin (odd's ratio = 1.90), serum CRP levels (odd's ratio = 2.11), and D-dimer (odd's ratio = 2.98). This is consistent with the findings stated by Shi et al. [33] reported that age ≥ 70 years was found to be an independent risk factor for in-hospital death for patients with diabetes as well as for patients without diabetes (hazard ratio (HR) 2.39 and 5.87, respectively).

In this study, at cut-off > 150 mg/dl, baseline serum CRP level had 63% overall accuracy in prediction of mortality among the studied with area under curve that was 0.674. Meanwhile, baseline D-dimer had 67.7% overall accuracy in prediction of mortality among the studied with area under curve that was 0.706. In a cohort conducted by Smilowitz et al. [34], including 2782 COVID-19 patients, CRP levels above 108 mg/L were associated with disease severity (47.6% vs 25.9%) and a higher mortality (32.2% vs 17.8%) (277). Similarly, in a retrospective study conducted by Sadeghi et al. [35] including 429 patients, it has been shown that not only the severe cases had significantly higher CRP levels than non-severe patients, but also that patients with CRP > 64.75 mg/L were more likely to have severe complications.

Limitations of this study were the relatively small sample size as the work had been conducted in a single center.

We recommend measuring another valuable inflammatory markers T17 and T33. Another valid radiological scoring system is required to classify severity of COVID-19 and correlate it with patient's outcome from the radiological point of view.

Conclusions

HRCT scan and measurement of CRP and ferritin plasma levels can be considered significant predictors for future prognosis and can early identify patients at risk of death and need for MV. Male gender, presence of DM, and chronic chest diseases are risk factors for severe illness.

Abbreviations

COVID19	Coronavirus disease
CORADS	Chest Disease Reporting And Data System
HRCT	Chest computed tomography
MV	Mechanical ventilation
RICU	Respiratory intensive care unit
CRP	C-reactive protein
LDH	Lactate dehydrogenase

Acknowledgements

None.

Authors' contributions

M.F and A.F contributed to the study design, conception, and manuscript revision. M.I contributed to literature search data collection and manuscript writing. (corresponding author) S.F contributed to statistical analysis, manuscript writing and revision.

Funding

None.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board and ethical committee of Faculty of Medicine, Assiut University in compliance with the Helsinki Declaration (IRB: 04–2024-300452).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 19 August 2024 Accepted: 8 October 2024
Published online: 14 October 2024

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