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Sarcopenia is associated with mortality in patients with COVID-19 independent of other demographic risk factors

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ABSTRACT

Objectives: To investigate whether sarcopenia had an effect on in-hospital mortality independent from other demographic characteristics in patients with Coronavirus disease 2019 (COVID-19), and to determine a reliable cut-off value for sarcopenia if there is such a relationship.

Methods: A total of 302 patients with COVID-19 were included in the study. Sarcopenia was assessed by indexed skeletal muscle mass at T12 vertebrae level (T12-SMI) on initial chest computed tomography (CT). A receiver operating characteristic (ROC) curve analysis was performed to detect a cut-off value of T12-SMI for mortality prediction. Then, sarcopenia was diagnosed by this value. Multivariable logistic regression analysis was used to detect independent variables for mortality.

Results: Patients were separated into groups; 26 (8.6%) patients in the mortality group and 276 (91.4%) patients in the no-mortality group. In ROC analysis, cut-off values of 34.06 cm²/m² (sensitivity: 70%, specificity: 77%) in males and 29.36 cm²/m² (sensitivity: 67%, specificity: 69%) in females for T12-SMI were computed for mortality prediction. There were 110 (36.4%) patients with sarcopenia. Sarcopenia was more frequent in the mortality group than the no-mortality group (73.1% vs 33%, $p < 0.001$). In multivariate analysis age, previous cardiovascular and respiratory disease, and sarcopenia were independently associated with mortality in COVID-19 patients.

Conclusions: A cut-off value of 34.06 cm²/m² in males and 29.36 cm²/m² in females for T12-SMI can be used to diagnose sarcopenia in patients with COVID-19. Sarcopenia is clearly associated with mortality in these patients.

Keywords: COVID-19, sarcopenia, mortality, computed tomography, skeletal muscle index

Coronavirus disease 2019 (COVID-19) caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) has led to a worldwide outbreak [1]. Until today, millions of people have been infected with the disease and still tens of thousands of people continue to caught the disease every day. Its clinical course varies from patient to patient and from asymptomatic situation to severe respiratory collapse

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and even death. Health care services in many countries have faced serious difficulties in responding to heavy patient burdens. Therefore, anticipating the people who have increased mortality rate is especially crucial to form an individual treatment plan and to manage healthcare resources efficiently. Some baseline demographic features such as older age, diabetes mellitus (DM), cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD) as well as laboratory parameters including elevated D-dimer have already been recognized as major determinants of worse prognosis in patients with COVID-19 [2-4].

Sarcopenia is diagnosed by the presence of low muscle quantity or quality, low muscle strength, and impaired physical performance [5]. It is known that sarcopenia is associated with impaired immune resistance and susceptibility to infectious diseases such as pneumonia [6, 7]. In addition, sarcopenia is associated with heart and respiratory diseases, DM, renal disease and increases the risk of hospitalization, and death [8-12]. These clinical problems are also firmly related with poor prognosis in patients with COVID-19 [2-4]. In the literature, there are a few studies with conflicting results regarding the impact of sarcopenia on adverse outcomes in patients with COVID-19 [13-15]. Moreover, there are no standardized values for the evaluation of sarcopenia in this population. Therefore, we had two purposes in this study; first, to investigate whether sarcopenia had an effect on in-hospital mortality independent from other demographic characteristics, and second, to determine a reliable cut-off value for sarcopenia if there is such a relationship.

METHODS

Patient Selection

Study population consisted of consecutive adult patients who applied to the COVID-19 outpatient clinic between December 1, 2020 and December 30, 2020 and were diagnosed with COVID-19 by reverse transcription-polymerase chain reaction (RT-PCR) test. Patients who underwent unenhanced chest computed tomography (CT) examination were included in the study but those with no or inadequate CT imaging were excluded from the study. In addition, those with no follow-up data for intensive care unit (ICU) admission, intubation, and mortality were also excluded from the study. Hypertension (HT), DM, CVD (coronary heart disease or heart failure), and COPD were diagnosed by the presence of the previous history and/or drug use.

The study was conducted in accordance with the guidelines in the Declaration of Helsinki. The study protocol was approved by our Local Research Ethics Committee and written informed consent was obtained for all of the participants. (the report number: 2011-KAEK-25 2020/11-11 of University of Health Sciences, Bursa Yüksek Ihtisas Training and Research Hospital Ethics Committee).

Clinical Examination

Patients were classified into four groups according to their clinical symptoms, signs, and chest imaging manifestations as being mild, moderate, severe, or critical COVID-19 cases:

1. Mild cases: mild or minimal clinical symptoms, no sign of pneumonia on chest imaging
2. Moderate cases: fever and respiratory symptoms, pneumonia on chest imaging
3. Severe cases: severe respiratory distress and/or increased respiratory rate ≥ 30 breaths/min and/or decreased oxygen saturation (SpO_2) on room air with ≤ 93 % and/or arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ≦ 300 mmHg
4. Critical cases: respiratory failure and requiring mechanical ventilation and/or septic shock and/or other organ failure requiring ICU admission [16].

Assessment of Sarcopenia and Chest Computed Tomography Imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) are accepted as gold standard methods to evaluate muscle quantity and quality [17]. Sarcopenia was assessed by chest CT obtained during the routine initial evaluation of patients with COVID-19. Chest CT images were acquired using a 64 slice multi-detector CT scanner (Somatom Sensation, Siemens, Germany). Initially, cross-sectional area (CSA, in cm^2) of all skeletal muscles at the level of the twelfth vertebrae (T12) were measured by using OsiriX Lite software (version 7.0.2, Pixmeo SARL, Bernex, Switzerland). The Hounsfield Units (HU) of -29 to +150 were used to isolate the skeletal muscle. Thus, the exact skeletal muscle area (T12-SMA, cm^2) was calculated based on HU, excluding vasculature

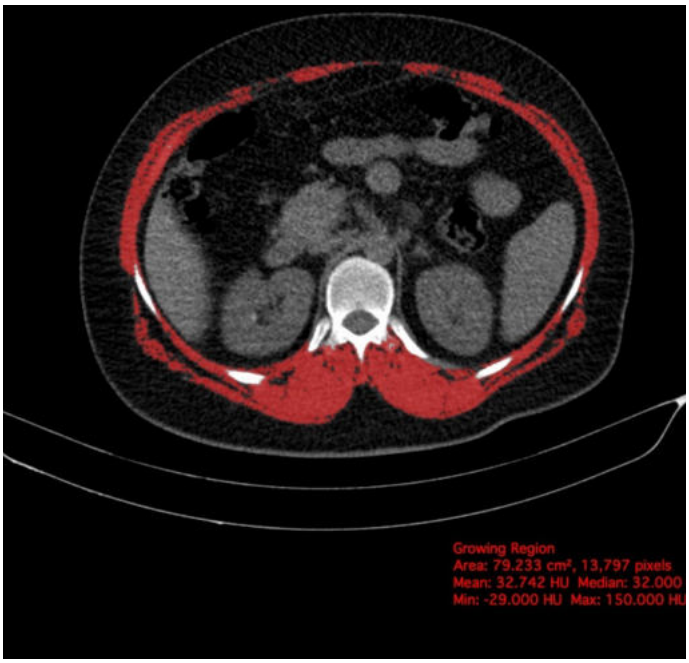

Fig. 1. T12-SMA measurement on chest CT image at the T12 vertebra level. Red zone indicating the crosssectional skeletal muscle area identified using a threshold of -29 to + 150 HU (T12-SMA 79.23 cm², T12-SMI 30.07 cm²/m²).

and fat infiltration (Fig. 1). Then, CSA measurements were normalized to patient size by dividing CSA with height in square meters to provide the skeletal muscle index (T12- SMI; cm2 /m2) [13, 14].

Study Endpoints

The main endpoint of the study was in-hospital mortality caused by COVID-19. The study population was separated into two groups as mortality (+) and mortality (-). In addition, the presence of ICU admission and intubation were determined second line endpoints of the study. Lastly, we created a combined end-point including mortality, ICU admission, and intubation.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as numbers and percentages. Normal distribution of continuous variables was evaluated by using the Kolmogorov-Smirnov test and histogram. Continuous variables were analyzed by independent-sample t-test or Mann-Whitney U test according to normal distribution. Chi-square and Fisher's exact tests were used for categorical variables. Receiver operating characteristic (ROC) curve analysis was performed to detect a cut-off value for sarcopenia diagnosis. Then, multivariable logistic regression analysis was used to detect independent demographic variables for mortality. Intra- and inter-observer variability was computed for reproducibility of T12-SMA by predefined Bland-Altman method [18, 19]. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were carried out by the SPSS 21 statistical software (SPSS Inc., Chicago, Illinois, USA).

RESULTS

A total of 302 patients were included in the study. There were 26 patients in the mortality group (8.6%) and 276 patients in the no-mortality group (91.4%). The baseline demographic and laboratory parameters of the study population were demonstrated in Table 1. DM, HT, CVD, and COPD were more frequent in the mortality group than the no-mortality group. T12-SMA, T12-SMI, age, C-reactive protein (CRP), white blood cell (WBC), and creatinine were higher but SpO_2 was lower in the mortality group than the no-mortality group. Intra- and inter-observer variability were assessed for T12-SMA and were found 4.9% and 6.8%, respectively.

In ROC analysis, cutt of values of 34.06 cm2/m2 (AUC = 0.758, $p = 0.002$, sensitivity 70%, specificity 77%) in males and 29.36 cm^2/m^2 (AUC = 0.772, $p = 0.001$,sensitivity 67%, specificity 69%) in females were detected for T12-SMI in association with mortality (Figs. 2 and 3). Then, patients with sarcopenia were determined in accordance with this cut-off value. Fifty (34.2%) of males and 60 (38.5%) of females had sarcopenia in the study population. Sarcopenia was more frequent in the mortality group than the no-mortality group (73.1% vs 33%, $p < 0.001$). Demographic features and end-points of patients with- and without sarcopenia were presented in Table 2. The patients with sarcopenia had more severe COVID-19 disease than those without sarcopenia. Hospitalization (53.6% vs 31.8%, $p < 0.001$), ICU admission (20.9% vs 7.3%, $p = 0.001$), intubation (18.2% vs 5.2%, $p < 0.001$) and combined end-point (21.8% vs 7.3%, $p < 0.001$) as well as mortality (17.3 vs 3.6%, $p < 0.001$) were more frequent in patients with sarcopenia than those without.

Table 1. Baseline demographic and laboratory variables of study population

	Mortality (+) (n = 26)	Mortality (-) (n = 276)	*p value*
Female gender, n (%)	13 (50)	143 (51.8)	1.0
Diabetes mellitus, n (%)	10 (38.8)	55 (19.9)	**0.04**
Hypertension, n (%)	16 (61.5)	72 (26.1)	**< 0.001**
CVD, n (%)	13 (50)	26 (9.4)	**< 0.001**
COPD, n (%)	7 (26.9)	18 (6.5)	**< 0.001**
Age, years	69.7 ± 11.1	51 ± 16.2	**< 0.001**
SpO_2 (%)	80.7 ± 12.6	95.9 ± 40.1	**< 0.001**
CRP (mg/L)	95.9 ± 58.8	29.9 ± 44.6	**< 0.001**
WBC ($\times 10^9$/L)	9.3 ± 6.8	6.5 ± 2.6	**0.01**
Creatinine (mg/dL)	1.3 ± 1.0	0.9 ± 0.7	**< 0.001**
T12-SMA (cm^2)	80.4 ± 23.5	98.1 ± 21.6	**0.001**
T12-SMI (cm^2/m^2)	28.7 ± 7.0	34.6 ± 6.3	**< 0.001**
Sarcopenia, n (%)	19 (73.1)	91 (33)	**< 0.001**

Data are shown as mean ± standard deviation or n (%). COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein, CVD = coronary artery disease and heart failure, SpO_2 = arterial blood oxygen saturation, T12SMA = spinal muscle area at T12 level, T12SMI = spinal muscle index at T12 level, WBC = white blood cell

The results of the univariate and multivariate analysis were shown in Table 3. In univariate analysis, age, DM, HT, COPD, CVD, and sarcopenia were associated with mortality. In multivariate analysis, age (OR: 1.051, 95% CI: 1.010-1.093, $p = 0.014$), COPD (OR: 5.731, 95% CI: 1.683-19.522, $p = 0.005$), CVD (OR: 5.246, 95% CI: 1.796-15.318, $p = 0.002$) and sarcopenia (OR: 6.091, 95% CI: 1.945-19.078, $p = 0.002$) were independently associated with mortality in patients with COVID-19.

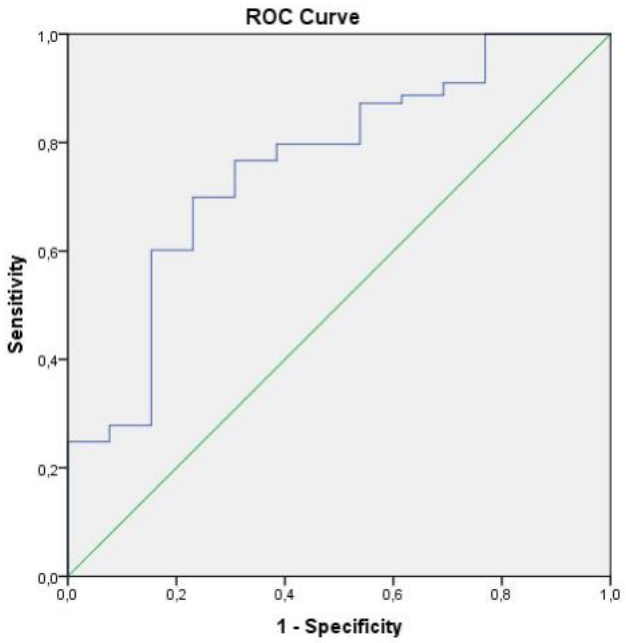

Fig. 2. ROC analysis for cut-off value of T12-SMI in male patients. AUC: 0.758, $p = 0.002$. Sensitivity 70%, spesicifity 77% for 34.06 cm^2/m^2 of T12SMI.

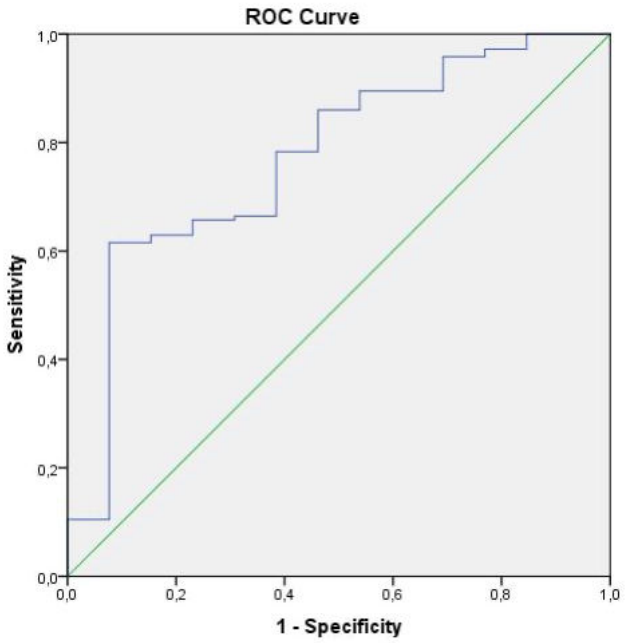

Fig. 3. ROC analysis for cut-off value of T12-SMI in female patients. AU: 0.772, $p = 0.001$. Sensitivity 67%, spesicifity 69% for 29.36 cm^2/m^2 of T12SMI.

Table 2. Baseline demographic and laboratory variables of patients with- and without sarcopenia

	Patients with sarcopenia (n = 94)	Patients without sarcopeina (n = 208)	*p value*
Age (years)	56.7 ± 19.3	50.3 ± 14.5	**0.003**
Female gender, n (%)	60 (54.5)	96 (50)	0.45
CRP (mg/L)	50.5 ± 61.9	27.0 ± 38.4	**0.025**
WBC ($\times 10^9$/L)	7.14 ± 3.5	6.5 ± 3.1	0.145
Ferritin (ng/mL)	416.7 ± 981.7	174.0 ± 172.9	**0.007**
D-dimer (µg/mL)	1.4 ± 2.6	0.7 ± 0.9	**0.06**
Diabetes mellitus, n (%)	22 (20)	43 (22.4)	0.63
Hypertension, n (%)	34 (30.9)	54 (28.1)	0.61
CVD, n (%)	16 (14.5)	12 (23)	0.52
COPD, n (%)	8 (7.3)	17 (8.9)	0.63
Disease severity, n (%)			
Mild	26 (23.6)	59 (30.7)	**< 0.001**
Moderate	45 (40.9)	106 (55.2)	
Severe	26 (23.6)	22 (11.5)	
Critical	13 (11.8)	5 (2.6)	
Hospitalization, n (%)	59 (53.6)	61 (31.8)	**< 0.001**
Pneumonia on CT, n (%)	84 (76.4)	133 (69.3)	0.19
Mortality, n (%)	19 (17.3)	7 (3.6)	**< 0.001**
Intubation, n (%)	20 (18.2)	10(5.2)	**< 0.001**
ICU admission, n (%)	23 (20.9)	14 (7.3)	**0.001**
Combined endpoint [&], n (%)	24 (21.8)	14 (7.3)	**< 0.001**

Data are shown as mean ± standard deviation or n (%). COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein, CT = computed tomography, CVD = coronary artery disease and heart failure, ICU = intensive care unit, WBC = white blood cell

[&] Combination of mortality, intubation and ICU admission

Table 3. Demographic predictors of mortality in patients with COVID-19

	Univariable analysis				Multivariable analysis			
	OR	95% CI		*p value*	OR	95% CI		*p value*
		Upper	Lower			Upper	lower	
Age	1.086	1.051	1.123	**< 0.001**	1.051	1.010	1.093	**0.014**
Gender	1.075	0.481	2.403	0.86				
DM2	2.51	1.080	5.838	0.03	1.049	0.360	3.057	0.930
HT	4.53	1.968	10.443	**< 0.001**	1.405	0.445	4.441	0.562
COPD	5.28	1.963	14.206	**0.001**	5.731	1.683	19.522	**0.005**
CVD	9.615	4.035	22.914	**< 0.001**	5.246	1.796	15.318	**0.002**
Sarcopenia	5.518	2.239	13.602	**< 0.001**	6.091	1.945	19.078	**0.002**

COPD = Chronic obstructive pulmonary disease, CVD = Coronary artery disease and heart failure, DM2 = Diabetes mellitus type 2, HT = Hypertension

DISCUSSION

In this study, we stated that sarcopenia is more frequent in patients with COVID-19 who died and it is independently associated with mortality in this population. In addition, sarcopenic COVID-19 patients had more severe disease and increased rate of hospitalization, ICU admission, and intubation than those without sarcopenia.

COVID-19 pandemic has led to millions of cases and death around the world. The clinical picture during COVID-19 disease is very variable that changes asymptomatic situation to life-threatening respiratory collapse because of pulmonary involvement. Moreover, the clinical course can show very sudden changes. Unfortunately, there is no effective and specific treatment method to quickly control the disease. Because of these factors, the patients were usually followed up in the hospital especially during the inital time of the pandemic. This pushed health care systems to their limits in many countries. Therefore, identifying individuals at high risk of poor prognosis has become crucial in managing health system resources effectively. Some demographic features such as older age, DM, CVD, COPD were quickly reported as worse prognosis indicators in patients with COVID-19 [2-4]. However, we still need to expand our knowledge about risk factors that have a negative effect on mortality because the COVID-19 pandemic is still continuing and health systems in some countries are facing serious challenges to compensate patient burden.

Sarcopenia is a relatively novel issue that reflects the presence of low muscle quantity or quality, low muscle strength, and low physical performance [5]. It is not only a part of musculoskeletal system disease but also is closely connected with other organ system disorders. Additionally, clinical evidence has shown that sarcopenic patients have impaired immune responses to infectious diseases [6]. These patients have a higher incidence of community-acquired pneumonia and nosocomial infection, and increased risk of infectious complications and poor prognosis [7, 20-22]. Some mechanisms were proposed to reveal the relationship between sarcopenia and susceptibility to infections and immune compromise. Skeletal mucle is currently considered as an organ breeding several solvable components (myokines) such as Interleukine (IL)-15 and IL-7 affording autocrine and paracrine reactions [23]. Beside promoting muscle regeneration and physiology, myokines also regulate immune reactions. For example, IL-15 promptes the reproduction and activity of natural killer (NK) cells and CD8+ (cytotoxic) T lymphocytes, also triggers stimulation and scavenging function of neutrophils [24, 25]. Likewise IL-7 is secreted from skeletal muscle cells and it provides the development and maintenance of immature lymphocytes [26]. Since NK cells and lymphocytes yield crucial protection against viral agents, the deficient of IL-15 and IL-7 expression might bring ineffective immunity for viral infections and SARS-CoV-2.

In addition, inflammation may play another pivotal role in the relationship between sarcopenia and negative results of COVID-19. It is known that sarcopenia is associated with chronic inflammation detected by increased blood level of CRP, Tumor Necrosis factor-α, and IL-6 [27]. Similarly, it is obvious that COVID-19 is caused by a hyperinflammatory response induced by SARS-CoV-2. In this study, both CRP and ferritin were higher in patients with sarcopenia than those without. Therefore, we thought that sarcopenia-related chronic inflammation may have a role in the development of adverse results in patients with COVID-19.

There are a few studies that investigated the relationship between sarcopenia and adverse end-points of COVID-19 [13-15]. Kim *et al*. [13] investigated prognostic effects of sarcopenia in patients with COVID-19 patients. They asserted that sarcopenia assessed by chest CT at T12 level was an independent predictor for delayed hospital discharge but not for mortality. Moctezuma-Velázquez *et al*. [14] also studied the relationship between sarcopenia and negative outcomes in patients with COVID-19. They reported that sarcopenia was not related to in-hospital mortality, need for intubation, and ICU admission. However, they diagnosed sarcopenia by using a predefined cut-off value which was established for patients with aortic valve stenosis. We thought that this led to a generalizability bias that affected their results. In other research, Feng *et al*. [15] evaluated the effects of sarcopenia detected by paraspinal muscle measurement on chest CT on composite end-point including death, ICU admission, and intubation in patients with COVID-19. They used median values of paraspinal

muscle index and density to assess sarcopenia and found its robust association with composite end-point including death, ICU admission, and intubation [15]. Our study has some differences from previous ones. First, we aimed to assess the prognostic effects of sarcopenia in association with only demographic features that can offer a simple and objective prognostic tool during this patients' initial clinical evaluation. Second, we computed a cut-off value for T12-SMI to diagnose sarcopenia in this population, specifically. There was no spesific cut-off value for patients with COVID-19 in the literature. And, every study used a different value (ie. median value or smallest quarter of T12-SMI) to evaluate the presence of sarcopenia that led to uncertainty. Thus, according to our results, we thought that this study may present a simple prognostic parameter for these patients' initial triage.

Limitations

This study has some limitations. First, this was not a randomized study. However, it should be accepted that a randomized study of COVID-19 in the case of the pandemic has some ethical issues. Therefore, we had to do this research observationally. Second, in the multivariable model, we used only demographic parameters as well as sarcopenia. However, we initially intended to seek the prognostic effect of sarcopenia as an imaging-based demographic feature and intended to evaluate a possible effect of sarcopenia on mortality as a demographic feature. Third, we could not assess the possible long term-effect of sarcopenia on mortality, because we did not have a long-term follow-up after hospital discharge. Therefore, further studies are needed to investigate this issue.

CONCLUSION

Sarcopenia is independently associated with mortality in patients with COVID-19. Hospitalization, ICU admission, and intubation encounter frequently in patients with COVID-19 who have sarcopenia. A cut-off value of 34.06 cm2/m2 in males and 29.36 cm2/m2 in females for T12-SMI can be used to diagnose sarcopenia in this population.

Authors' Contribution

Study Conception: ME, DA, HES; Study Design: ME, DA, HES, MG; Supervision: DT, MG; Funding: N/A; Materials: N/A; Data Collection and/or Processing: ME, MG; Statistical Analysis and/or Data Interpretation: DA, HES; Literature Review: ME, DA, HES; Manuscript Preparation: ME, DA, MG and Critical Review: ME, DA, DT, MG.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

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